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REPORT
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FOOD AND DRUG ADMINISTRATION MODERNIZATION AND ACCOUNTABILITY ACT OF 1997

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Mr. JEFFORDS, from the Committee on Labor and Human Resources, submitted the following

REPORT

together with

ADDITIONAL AND MINORITY VIEWS

[To accompany S. 830]

The Committee on Labor and Human Resources, to which was referred the bill (S. 830) to amend the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act to improve the regulation of food, drugs, and biological products, and for other purposes, having considered the same, reports favorably thereon with an amendment in the nature of a substitute and recommends that the bill (as amended) do pass.

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39–010

I. PURPOSE AND SUMMARY

Under the Federal Food, Drug, and Cosmetic Act (FFDCA), the Food and Drug Administration (FDA) has two important functions: (1) the review and approval of important new products that can improve the public health, such as lifesaving drugs, biological products, and medical devices; and (2) the prevention of harm to the public from marketed products that are unsafe or ineffective. Since 1938, the Federal Food, Drug, and Cosmetic Act has been amended numerous times to strengthen the FDA's function of ensuring that unsafe or ineffective products are not marketed but has been changed only once, by the Prescription Drug User Fee Act of 1992 (PDUFA), to strengthen the FDA's function of reviewing and approving important new products that can improve the public health.

The Food and Drug Administration Modernization and Accountability Act of 1997, S. 830, is designed to ensure the timely availability of safe and effective new products that will benefit the public and to ensure that our Nation continues to lead the world in new product innovation and development. The legislation accomplishes three major objectives: it builds upon recent administrative reforms that both streamline FDA's procedures and strengthen the agency's ability to accomplish its mandate in an era of limited Federal resources; it requires a greater degree of accountability from the agency in how it pursues its mandate; and it provides for the reauthorization of PDUFA.

The FDA acknowledges that its mandate requires it to regulate over one-third of our Nation's products. Within its purview the FDA regulates nearly all of the food and all of the cosmetics, medical devices and drugs made available to our citizens. This legislation identifies areas where improvements can be made that will strengthen the agency's ability to approve safe and effective products more expeditiously. It builds upon the numerous investigations by Congress, the FDA, the General Accounting Office (GAO), and other organizations that have identified problems with the current FDA product approval system and have recommended reasonable reforms to streamline and strengthen that system. It includes the following major provisions:

1. THE LEGISLATION ESTABLISHES A CLEARLY DEFINED, BALANCED MISSION FOR THE FDA

Congress has never established a mission statement for the FDA. The FDA in March of 1993 adopted a formal statement declaring that the agency "is a team of dedicated professionals working to protect and promote the health of the American people." Although this statement defines the agency's mission in terms of ensuring that the products it regulates comply with the law, there is no reference to the importance of approving new products that benefit the public. The legislation amends the Food Drug and Cosmetic Act by adding an agency mission statement focused on: (1) protecting the public health by ensuring that the products it regulates meet the appropriate FDA regulatory standards, (2) promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a manner which does not

unduly impede innovation or product availability, and, (3) participating with other countries to reduce regulatory burdens, harmonize regulatory requirements, and achieve appropriate reciprocal arrangements with other countries.

2. THE LEGISLATION IMPROVES PATIENT ACCESS TO NEEDED THERAPIES AND PROVIDES EXPEDITED HUMANITARIAN ACCESS TO MEDICAL DEVICES

The FDA has no crosscutting program that ensures access by patients with serious or life-threatening diseases to drugs or devices in clinical trials—even when that unapproved therapy may be the only way to save the patient's life. The legislation would create new law whereby manufacturers may provide, under strictly controlled circumstances and in response to a patients request, an investigational product for those patients needing treatment for a serious or life-threatening disease. The legislation also improves the existing program for the humanitarian use of medical devices for patient populations of fewer than 4,000.

3. THE LEGISLATION CREATES NEW INCENTIVES FOR DETERMINING BETTER PHARMACEUTICALS FOR CHILDREN

Children have for years been wrongly considered "small adults" when estimating the effect of prescription drugs on their overall health. Currently there is no systematic means for testing the safety and efficacy of drugs on the pediatric population. The legislation gives the Secretary authority to request pediatric clinical trials for new drug applications and provides 6 extra months of market exclusivity to drugs when the manufacturer voluntarily meet certain conditions under the program. The Secretary must determine in writing that information relating to the use of a drug in the pediatric population is needed. In addition, the FDA may establish time frames for completing such pediatric studies before additional exclusivity is granted.

4. THE LEGISLATION GIVES PATIENTS ACCESS TO NEW THERAPIES MORE QUICKLY THROUGH A NEW "FAST-TRACK" DRUG APPROVAL PROCESS

For several years the FDA has allowed the expedited review and approval of drugs but such review has been largely confined to treatments for HIV/AIDS or cancer. This provision facilitates development and expedites approval of new drugs for the treatment of any serious or life-threatening diseases.

5. THE LEGISLATION INCREASES ACCESS TO INFORMATION BY HEALTH PROFESSIONALS AND PATIENTS

For years, sophisticated users of health related economic information, like health maintenance organizations, have been constrained from access to important information that could help them reduce health-care costs. The legislation would apply the Federal Trade Commission's "competent and reliable scientific evidence" standard for FDA review of health care economic statements distributed by manufacturers to sophisticated purchasers. In the past, only a few patient groups have had access to information about on-

going clinical trials for lifesaving therapies. The legislation expands patient access to information by requiring the creation of databases on ongoing research related to the treatment, detection, and prevention of serious or life-threatening diseases.

6. THE LEGISLATION INCREASES AGENCY ACCESS TO EXPERTISE AND RESOURCES

Current law contains no provisions to assure that the FDA can access expertise housed at the National Institutes of Health (NIH) and other science-based Federal agencies to enhance the scientific and technical expertise available to FDA's product reviewers. The legislation requires FDA to develop programs and policies to foster such collaboration. The legislation also authorizes the agency to contract with outside experts to review all or parts of applications when it will add to the timeliness or quality of a product review, and provides for the use of accredited outside organizations for the review of medical devices.

7. THE LEGISLATION IMPROVES THE CERTAINTY AND CLARITY OF RULES

The legislation makes a series of changes related to the classification, review and approval of FDA regulated products designed to ensure that sponsors of new products face consistent and equitable regulatory requirements. In addition, the legislation gives FDA 2 years to evaluate the success of its recently issued "Good Guidance Practices" guidance after which FDA is required to implement this policy as a regulation, making any modifications necessary to reflect experience during the 2-year trial period.

The legislation provides medical device manufacturers with the ability to make recommendations to the FDA respecting initial product classifications. It facilitates the reclassification and/or approval of device applications by allowing FDA to consider historical data in making its determinations, and the legislation more clearly states the relationship of labeling claims to approval and clearance of medical devices. It increases the certainty of review time frames by providing a definition of a day with respect to the agency's "review time clock" and by requiring the agency to approve or disapprove a device application within 180 days.

The legislation also prohibits FDA from withholding the initial classification of a device because of a failure to comply with any provision of the unrelated to making a determination of substantial equivalence, and it clarifies that FDA has discretion in determining the number of clinical trials required for the approval of a drug or device. FDA would retain total discretion to require a sufficient number of trials to show safety and efficacy. The provision introduces the concept that two trials are not always necessary, establishes the primacy of quality data over quantity of data, and requires the FDA to consider the number and type of trials on a product-by-product basis.

8. THE LEGISLATION IMPROVES AGENCY ACCOUNTABILITY AND PROVIDES FOR BETTER RESOURCE ALLOCATION BY SETTING PRIORITIES

Except as required under PDUFA, the FFDCA provides no form of public accountability by the FDA for its performance of its statutory obligations. The legislation requires FDA to develop a plan designed to: (1) minimize deaths and injuries suffered by persons who may use products regulated by the FDA; (2) maximize the clarity and availability of information about the product review process; (3) implement all inspection and post-market monitoring provisions of the Act by 1999; (4) ensure access to the scientific and technical expertise necessary to properly review products; (5) establish a schedule to bring the FDA into compliance by 1999 with the product review times in the Act for products submitted after the date of enactment of this section; and (6) eliminate the backlog of products awaiting final action by the year 2000. The legislation also requires FDA to submit an annual report to assist Congress in assessing the agency's performance in accomplishing the objectives laid out in the agency plan.

The legislation streamlines several FDA functions with respect to certain review and inspection processes thus allowing the agency to focus its limited resources on areas of greatest need. The legislation provides FDA with the discretion to approve drugs and biologics on the basis of products manufactured in pilot and small-scale facilities. FDA is also directed to establish policies to facilitate the approval of supplemental applications for new uses for an approved product. Further, the legislation establishes procedures and policies to foster a collaborative review process between the agency and the sponsors of medical device applications. Finally, the legislation streamlines the review of minor modifications to medical devices.

9. THE LEGISLATION SIMPLIFIES THE APPROVAL PROCESS FOR INDIRECT FOOD CONTACT SUBSTANCES AND PROVIDES A MORE REASONABLE STANDARD FOR SOME HEALTH CLAIMS

Current law requires the agency to preapprove food contact substances, most of which pose little if any risk to human health. The legislation replaces the preapproval process for these substances (primarily packaging materials) with a simple notification requirement. The legislation also provides for health claims for foods, with premarket notification, when the claims are based on authoritative recommendations by an authoritative scientific body of the U.S. Government such as the National Institutes of Health, the Centers for Disease Control and Prevention, or the National Academy of Sciences.

10. THE LEGISLATION REAUTHORIZES THE PDUFA PROGRAM THUS ENSURING ADDITIONAL RESOURCE AVAILABILITY FOR THE AGENCY

PDUFA is reauthorized for 5 years. Performance goals beyond those set for the 1992 Act will be identified in side letters between the FDA and the Senate Committee on Labor and Human Resources. The bill assumes that FDA will receive for fiscal year 1998 the 1997 level of appropriated funds for the agency. For fiscal years 1999 through 2002, the bill assumes an annual inflation adjustment.

II. Background and Need for the Legislation

A. BACKGROUND

Over the years, Congress has dramatically expanded the reach and responsibilities of the FDA. The Federal Food and Drugs Act of 1906, the first national statute enacted by Congress to regulate the American food and drug supply, gave the Agency the authority to police the market and remove adulterated or misbranded foods and drugs.

In 1938, Congress passed the Federal Food, Drug, and Cosmetic Act, which expanded the agency's reach to the regulation of cosmetics and medical devices and, for the first time, provided the agency with the authority to review and assure the safety of a product—new drugs—prior to the marketing of that product. The 1938 statute required sponsors of new drugs to file a new drug application notifying the FDA prior to marketing a new human or animal drug. The new drug application became effective after 60 days (which could be extended to 180 days), unless the Agency found that it had insufficient information to determine whether the drug was safe for its intended use.

In the ensuing years, Congress enacted a series of statutes further expanding the FDA's regulatory reach. These included the 1944 Pitts Act, which gave the FDA the authority to regulate biological products, and the Miller Pesticide Amendments of 1954, which required FDA premarket approval for pesticides in or on raw or processed foods. The Food Additive Amendment of 1958 required premarket approval of food additives, and the Color Additive Amendments of 1960 required premarket approval of color additives in food, drugs, and cosmetics. The Drug Amendments of 1968 consolidated the premarket approval requirements for new animal drugs and feed additives. The Medical Device Amendments of 1976 created a device ranging from the most simple to the most complex and premarket approval for new medical devices, and the Safe Medical Devices Act of 1990 codified FDA's premarket notification program and increased the agency's postmarket enforcement capabilities.

From 1906 to the present, then, the FDA's role has expanded from one of removing adulterated or misbranded products from the market to one of preapproving the testing and marketing of products.

B. NEED FOR THE LEGISLATION

Over the years, and particularly with the enactment of requirements that the FDA determine that drugs and devices are effective as well as safe, the FDA's requirements for clinical testing and its premarket reviews of new products have grown increasingly complex, time-consuming, and costly. From the 1960's to the 1990's, for example, the time required to complete clinical trials for new drugs has grown from 2.5 to nearly 6 years. Applications for the approval of new drugs typically run to hundreds of thousands of pages in length. According to a recently published study, from the beginning of the process to the end, it takes an average of 15 years and costs in the range of $500 million dollars to bring a new drug to market.

[DiMasi, Trends in Drug Development, Costs, Times, and Risks, 29 Drug Information Journal 375, 382, April–June 1995.]

By law, the FDA is required to review and act on applications for the approval of new drugs and devices within 180 days. According to the FDA's own budget justification for fiscal year 1998, it takes the agency an average of 12 months longer than the statute allows for the agency to review new drugs and three and one-half months longer than the statute allows for premarket approval (PMA) devices. And the agency in its budget submission to Congress for FY 1998 projects that the backlog for devices is projected to increase by 17 percent from this year to next.

These increases in the time, complexity, and cost of bringing new products to market are borne directly by the public, in delayed access to important new products—including life-saving medical therapies—and in higher costs. They are a growing disincentive to continued investment in the development of innovative new products and a growing incentive for American companies to move research, development, and production abroad, threatening our Nation's continued world leadership in new product development, costing American jobs, and further delaying the public's access to important new products.

Over the past 20 years, a bipartisan consensus has emerged on the need for reforms of the FDA premarket approval process to strike a better balance between the need to ensure that products are safe and effective, on the one hand, and to facilitate the timely availability of new products, on the other.

During 1978 and 1979, Congress considered a wholesale revision of the new drug approval process. This committee led that effort, reporting legislation introduced by Senator Kennedy, the Drug Regulation Reform Act of 1979. That legislation was subsequently approved by the Senate but was not considered by the House of Representatives. A number of the provisions in that legislation are reflected in S. 830, including provisions to permit new drug sponsors to obtain advice from the agency regarding their investigational plans; to require the FDA to issue written guidelines regarding protocols and methods for conducting drug investigations; and to require the FDA to take measures to ensure that reviews are conducted efficiently and expeditiously.

Many of these same changes were recommended by the Commission on the Federal Drug Approval Process, convened at the request of then-Representative Albert Gore, Jr., chairman of the House Subcommittee on Investigations and Oversight and then-Representative James Scheuer, chairman of the House Subcommittee on Natural Resources, Agricultural Research and Environment. The Commission's 1982 report recommended such changes as simplification of the investigational new drug requirements; recognition that drug effectiveness could be demonstrated by one study in appropriate cases; greater utilization of outside expert advice; improving interactions with industry; tracking the review process to ensure timeliness; simplified procedures for the use of investigational drugs for therapeutic purposes; greater reliance upon expert judgment in determining the safety and effectiveness of drugs; concurrent review of portions of new drug applications by FDA; and

greater reliance on foreign studies. Some of the Commission's recommendations are incorporated in S. 830.

In 1988, concern about the slow process for the development and approval of AIDS and cancer drugs led to the establishment, under the auspices of the President's Cancer Panel, of a National Committee to Review Current Procedures for Approval of New Drugs for Cancer and AIDS. The committee's final report, issued in 1990, recommended a national policy to foster the development of new drugs for AIDS and cancer; expediting approval of important new drugs; greater use of scientific judgment of qualified experts in determining the effectiveness of new drugs; the use of surrogate end points to establish drug effectiveness; a more open relationship between the FDA and the regulated industry in order to foster a spirit of mutual cooperation; responsiveness to the needs of patient advocacy groups; a fundamental restructuring of the FDA advisory committee system; more flexible use of investigational drugs for treatment; the right of patients to obtain investigational drugs under expanded access conditions; greater use by the FDA of outside review of new drug applications; and automatic approval of supplemental new drug applications for minor technical changes such as manufacturing modifications. Again, many of these recommendations are incorporated in S. 830.

In 1989, in response to serious questions that were being raised about the ability of the FDA to perform its job, Secretary of Health and Human Services, Dr. Louis Sullivan, chartered the Advisory Committee on the Food and Drug Administration. The committee was chaired by Dr. Charles Edwards, a former FDA commissioner. Dr. David Kessler served on the committee until his appointment as FDA commissioner. The charter directed the committee to examine the mission, responsibilities, and structure of the FDA and to make recommendations for improving the agency's operations.

One of the major findings of the committee was the need for the FDA to set forth a clear statement of its mission and goals and a plan for achieving the goals. In formulating a statement of purpose and program goals, the committee found that—

> * * * the agency should be guided by the principle that expeditious approval of useful and safe new products enhances the health of the American people. Approving such products can be as important as preventing the marketing of harmful or ineffective products. This is especially true for people with life-threatening illnesses and for diseases for which alternative therapies have not been approved.

This key recommendation underlies the legislation's Mission Statement and many of the provisions found in S. 830.

In 1991, The Council on Competitiveness, chaired by Vice President Dan Quayle, announced an important administration initiative to improve the FDA's drug approval process. The initiative was designed to achieve three overarching goals by 1994—a substantial reduction in the average development and approval time for all new drugs; a reduction in FDA approval time for important new drugs to 6 months; and a reduction in FDA approval time to 12 months for all other drugs.

The Council on Competitiveness also recommended a number of specific reforms, including expanded use of outside reviews; expanded use of advisory committees; flexible interpretation of the efficacy standard; accelerated approval through a reduction in the number of clinical studies required prior to approval and the amount of time FDA requires to grant approval, including reliance on surrogate endpoints; enhanced computerization to track applications and expedite review; and enhanced internal management, including the measurement of progress in application review against statutory deadlines. Many of these recommendations are incorporated in S. 830.

Most recently, Vice President Gore has pressed for reform of the FDA product approval system as part of President Clinton's Reinventing Government initiative. The President and Vice President have issued six reports, covering drugs and medical devices, drugs made from biotechnology, food, and cancer drugs, animal drugs, and human tissue. The administrative reforms and recommendations in these reports are designed to improve the product approval system, eliminate outmoded regulations, and update the Federal Food, Drug, and Cosmetic Act to reflect advances in the science of new product development and testing. Many of the recommendations in these reports are incorporated in S. 830.

During the 104th Congress, the committee held four hearings on reforming the FDA. The witnesses—several of whom had served on these advisory panels—testified about the same problems that have been described in the reports summarized above and recommended many of the same solutions. As a result of those hearings the committee last year reported legislation with strong bipartisan support, S. 1477, that would have incorporated many of the recommendations discussed above. In addition, during the 104th Congress, action was taken to better acknowledge the global marketplace and facilitate United States manufacturer's ability to get medical products to doctors and patients overseas through passage of the Food and Drug Export Reforms contained in P.L. 104–134.

Most recently, this committee has continued the effort to modernize and bring greater accountability to the FDA. The committee held two hearings in early 1997. During the first the committee received testimony from the lead FDA Deputy Commissioner, Dr. Michael Friedman, and all of the FDA Center Directors. The second hearing included representatives from patient and consumer coalitions and from the food, drug, and medical device sectors regulated by the FDA.

The committee learned from the administrative reforms and the progress it has already undertaken, areas that remain a challenge, and those areas that require legislative authority to change.

The committee listened to consumers' concerns about provisions that were considered last year that they felt would weaken the FDA's ability to protect the public health. Finally, the committee learned of the ongoing and needless delays and frustrations facing the health care and consumer product sectors of our economy in working with the FDA. The committee learned of the frustrated attempts to work through the bureaucratic maze of needless regulatory delays—delays that prohibited people from getting access to vitally needed, life saving medical treatments, drugs and devices.

Every administration in the past 20 years has recognized the need for modernizing the FDA's product approval system to bring into better balance the need to ensure the safety and effectiveness of products and the need to facilitate the development, testing, and timely approval of safe and effective products that benefit the public. Until recently, the FDA has been very slow to respond, or has not responded at all, to recommendations for reform made by the distinguished advisory panels that have been convened over the years.

America's pharmaceutical, biotech, medical device, and food industries are among our most innovative, dynamic, and productive. They contribute significantly to our Nation's high standard of health care and to our unparalleled supply of wholesome, abundant, and affordable food. They hold the promise of further breakthroughs in life-saving and enhancing therapies to combat the diseases and disabling conditions afflicting us today and those which may emerge in the future. They hold the promise of new food technologies that will enhance diets and improve health, provide natural resistance to pests, droughts, and other plagues, and help meet the nutritional needs of a growing world population. They are job-creating industries that contribute positively to our balance of trade.

Formidable challenges must be met, however, if these opportunities are to be realized and America is to continue to lead the world in product innovation. Domestically, our health care system is rapidly reorganizing, consolidating, and moving into managed care, with potentially profound effects on the market for products and the revenues necessary for continued research and product development. International markets are becoming increasingly competitive, particularly as the European Union moves to adopt a uniform drug and device approval system.

If we are to confront these challenges and realized the opportunities on today's and tomorrow's horizons, we cannot afford an overly complex, bureaucratic, time-consuming, and expensive regulatory system. Nor can we afford an adversarial relationship between the FDA and the industries it regulates or an agency pursuing so many agendas that it lacks a clear-cut mission and sphere of responsibility. We must update our food and drug laws and our regulatory practices to reflect the scientific and technological advances that have occurred in the development and testing of new products and to ensure that the FDA is an agency committed to fostering innovation and ensuring timely public access to beneficial new products.

It is no easy task that Americans ask FDA to perform. Americans want it to hold the gate to the market tightly shut against unsafe or ineffective products while opening it wide for the next generation of innovation—with all of its potential promise, but not without its risks. Clear statutory guidance is needed to assist the Agency to find this delicate balance and to bring our food and drug laws and regulatory systems into the next century. The FDA Modernization and Accountability Act of 1997, S. 830, embodies many of the bipartisan conclusions and recommendations reached by the expert panels for accomplishing this difficult task of balancing risk and promise.

III. Legislative History and Votes in Committee

"The Food and Drug Administration Modernization and Accountability Act of 1997," S. 830, was introduced by Senator Jeffords on June 5, 1997. Prior to the drafting of the legislation, the committee held 2 days of hearings: on March 19 and April 11, 1997, entitled "Addressing the FDA's Performance, Efficiency, and Use of Resources." These hearings examined the challenges and opportunities facing our Nation's pharmaceutical, biotech, medical device, and food industries and ways that the FDA's regulation of these industries might need to be reformed to ensure that these challenges are met and opportunities realized.

On June 11 and 18, 1997, the committee held executive sessions to consider S. 830. Senator Jeffords offered an amendment in the nature of a substitute that was considered as original text for purposes of further amendment. Thirteen additional amendments were considered in the executive sessions and the substitute as amended was adopted on a roll call vote of 14 yeas to 4 nays. S. 830, as amended, was approved by voice vote.

A. Amendments and Motions Adopted by Voice Vote During Executive Sessions

Six amendments were adopted in the executive sessions by voice vote and one amendment was adopted by unanimous consent.

1. Senator Kennedy offered an amendment to section 609 to clarify key definitions of radiopharmaceuticals. The bill provided that the Secretary shall, within 18 months after enactment of this Act, promulgate regulations that shall provide that the determination of the safety and effectiveness of a radiopharmaceutical shall include, but not be limited to, consideration of the proposed use of the radiopharmaceutical in the practice of medicine, the pharmacological and toxicological activity of the pharmaceutical (including any carrier or ligand component of the radiopharmaceutical), and the estimated absorbed radiation dose of the radiopharmaceutical. These standards were further clarified by Senator Kennedy's amendment.

2. Senator Kennedy offered an amendment to section 613 which provides for the expedited approval of certain drugs intended for the treatment of serious or life-threatening conditions. The amendment provides that approval of drugs under this "fast track" process may be subject to a requirement that the sponsor submit copies of all promotional materials related to the fast track drug during the preapproval review period and, following approval, at least 30 days prior to dissemination of the materials for such period of time as the Secretary deems appropriate. In addition, the amendment clarifies the conditions under which incomplete applications may be accepted for filing review, establishes expedited procedures for the withdrawal of approval of a fast track drug, and, provides that within 1 year after enactment of this Act the Secretary shall issue guidance describing the policies and procedures related to fast track drugs.

3. Senator Dodd offered an amendment to the Public Health Service Act that would establish, under a new section 807, a one-

stop shopping information service for individuals with serious or life-threatening diseases.

4. Senator Jeffords offered an amendment to modify a series of amendments that had been filed June 11 for which further agreement had been reached.

5. Senator Kennedy offered an amendment to strike section 611 of S. 830 relating to supplemental applications for the approval of new uses of approved drugs and devices and replace that section with alternative provisions to improve the FDA's supplemental application review process.

6. Senator Hutchinson offered an amendment to authorize and clarify provisions related to the pharmacy compounding of drugs.

7. Senator Gregg offered an amendment related to health claims for food products that was accepted by unanimous consent as a modification of the health claims language included in S. 830. The provision extends from 90 to 120 the number of days a person would be required to submit to the Secretary a notice of the health claim prior to first introduction of the health claim into interstate commerce. The amendment also clarifies that false and misleading claims are prohibited under section 403(a) of the Act, and that "significant scientific agreement" is required as the basis for a health claim, as required by section 403(r)(3)(B) of the Act. In addition, the amendment clarifies that the Secretary may undertake rulemaking to stop the use of a claim, or go to court in an enforcement proceeding, at any point in time.

B. ROLLCALL VOTES TAKEN DURING THE EXECUTIVE SESSIONS

Six rollcall votes on amendments were taken during the executive session:

1. Senator Kennedy offered an amendment to strike the provisions related to health claims for food products. The amendment was defeated by a rollcall vote of 5 yeas to 13 nays.

Yeas	Nays
Kennedy	Jeffords
Bingaman	Coats
Wellstone	Gregg
Murray	Frist
Reed	DeWine
	Enzi
	Hutchinson
	Collins
	Warner
	McConnell
	Dodd
	Harkin
	Mikulski

2. Senator Gregg offered an amendment to prohibit State and local governments from establishing or continuing any requirement relating to the regulation of nonprescription drugs or cosmetics which is different from, or in addition to, or otherwise not identical with Federal requirements. The amendment permits States to apply to the Secretary for an exemption from the prohibition and propose a requirement which is justified by protecting an important public interest that would otherwise be unprotected, that would not cause the nonprescription drug or cosmetic to be in violation of any applicable requirement or prohibition under Federal law, and that would not unduly burden interstate commerce. The amendment was adopted on a rollcall vote of 15 yeas to 3 nays.

Yeas	Nays
Jeffords	DeWine
Coats	Kennedy
Gregg	Murray
Frist	
Enzi	
Hutchinson	
Collins	
Warner	
McConnell	
Dodd	
Harkin	
Mikulski	
Bingaman	
Wellstone	
Reed	

3. Senator Kennedy offered an amendment to provide the FDA with authority to level civil monetary penalties for failure of a company to perform post-approval research. The amendment was defeated by a rollcall vote of 6 yeas to 12 nays.

Yeas	Nays
Kennedy	Jeffords
Wellstone	Coats
Bingaman	Gregg
Murray	Frist
Reed	DeWine
	Enzi
	Hutchinson
	Collins
	Warner
	McConnell
	Dodd
	Harkin
	Mikulski

4. Senator Harkin offered an amendment to the provision pertaining to the review of medical device applications by organizations accredited by the FDA. Senator Harkin's amendment would have required the Secretary to check for conflicts of interest and review the terms of compensation between the accredited party reviewer and the manufacturer of the product to be reviewed. Prior to the roll call vote, Senator Harkin modified his amendment by clarifying that the Secretary would have the authority to review the terms of the compensation, but not be required to do so. The amendment was defeated on a rollcall vote of 8 yeas to 10 nays.

Yeas	Nays
Kennedy	Jeffords
Dodd	Coats
Harkin	Gregg
Mikulski	Frist
Bingaman	DeWine
Wellstone	Enzi
Murray	Hutchinson
Reed	Collins
	Warner
	McConnell

5. Senator Harkin offered an amendment to: (1) limit scope of reviews of medical devices by organizations accredited by the FDA to devices for which the agency has not required clinical data, (2) limit the scope to devices for which the agency has prepared vertical standards or guidance documents, and (3) reduce by half the number of devices required to be eligible for the pilot. The amendment was defeated by a rollcall vote of 6 yeas to 12 nays.

Yeas	Nays
Kennedy	Jeffords
Harkin	Coats
Bingaman	Gregg
Wellstone	Frist
Murray	DeWine
Reed	Enzi
	Hutchinson
	Collins
	Warner
	McConnell
	Dodd
	Mikulski

6. Senator Jeffords offered the substitute as amended by the committee and it was passed on a rollcall vote of 14 yeas to 4 nays.

Yeas	Nays
Jeffords	Kennedy
Coats	Harkin
Gregg	Bingaman
Frist	Reed
DeWine	
Enzi	
Hutchinson	
Collins	
Warner	
McConnell	
Dodd	
Mikulski	
Wellstone	
Murray	

C. FOUR AMENDMENTS OFFERED AND SUBSEQUENTLY WITHDRAWN

1. Senator McConnell offered and then withdrew two amendments related to food labeling.

2. Senator Gregg offered and then withdrew an amendment to modify the drug fees provision.

3. Senator Harkin offered and then withdrew an amendment to permit an individual to be treated by a health care practitioner with any method of medical treatment such an individual requests.

IV. Explanation of the Legislation and Committee Views

TITLE I—IMPROVING PATIENT ACCESS

Mission

The first title of S. 830 establishes in statute that the mission of the FDA is to protect the public health by ensuring that foods are safe, wholesome, and sanitary; human and veterinary drugs are safe and effective; there is a reasonable assurance of safety and effectiveness of devices intended for human use; cosmetics are safe and properly labeled; and the public health and safety are protected from electronic product radiation. In addition, the FDA shall promptly and efficiently review clinical research and take appropriate action on the marketing of regulated products in a manner that does not unduly impede innovation or product availability. The FDA shall participate with other countries to reduce the burden of regulation, to harmonize regulatory requirements, and to achieve appropriate reciprocal arrangements.

The committee concurs with the view of the Advisory Committee on Food and Drug Administration (discussed above) that "the agency should be guided by the principle that expeditious approval of useful and safe new products enhances the health of the American people. Approving such products can be as important as preventing the marketing of harmful or ineffective products."

From the 1906 Food and Drugs Act through the 1990 Safe Medical Devices Act, food and drug law has emphasized that the duty of the FDA is to protect the public against unsafe or ineffective

products. The purpose of this legislation, as reflected in the mission statement, is to continue protection of the public against unsafe or ineffective products while providing a better balance in the law by ensuring timely access to safe and effective products.

Expanded access to investigational therapies

For many years, the need for patients to have access to unapproved therapies went unrecognized under the Federal Food, Drug and Cosmetic Act. The FDA established informal policies relating to compassionate use of investigational products shortly affer enactment of the 1938 Act, but these policies remained informal and outside FDA regulations.

Recently the FDA has established programs some of which are embodied in regulation, to make investigational drugs and devices available to patient with serious and life-threatening conditions and to patients in emergency situations. Most (but not all) such programs have resulted in access to promising new investigational and experimental therapies for HIV/AIDS and cancer. The committee commends the FDA for adopting these needed programs but the committee wishes to provide statutory direction to expanded access programs and emphasize that opportunities to participate in expanded access programs are available to every individual with a life-threatening or seriously debilitating illness for which there is not an effective, approved therapy.

The legislation establishes in statute that any person, acting through a licensed physician, may request access to an unapproved investigational drug or device, and that any manufacturer or distributor may provide that unapproved product, if it is for the diagnosis, monitoring, or treatment of a serious disease or condition, an immediately life-threatening or seriously debilitating disease or condition, or any other disease or condition designated by the FDA as appropriate for expanded access. The Secretary is given oversight over key aspects of this process to ensure that there is sufficient evidence of safety and efficacy to support the use of the investigational drug or device outside of a clinical trial. Further, the Secretary must determine that expanded access will not interfere with the adequate enrollment of patients into clinical trials for the testing of the drug or device.

The physician must determine that a patient has no comparable or satisfactory alternative and that the risk from the investigational product is not greater than the risk from the disease. An exemption for the investigational drug or device must be in effect under the FFDCA. The manufacturer must be pursuing marketing approval with due diligence. A manufacturer or distributor may decline to make an investigational product available under such a program.

Consistent with the desire of the committee to help ensure that patients with serious conditions and no realistic alternative treatment shave available to them investigational products that may offer some promise of help, the legislation requires the Commissioner to inform the medical profession and such groups as voluntary health associations about the availability of investigational products for expanded access use. Too often, patients and their physicians are unaware that new drugs and devices are under in-

vestigation and are available for expanded use pending review by the FDA. This provision will help to ensure that all patients will have equal knowledge of and access to investigational products.

The committee emphasizes that it has purposely used broad language in this section relating to "serious" conditions, without attempting to define them, in order to permit wide flexibility in implementation. Illnesses that do not cause death can nonetheless destroy the lives of both patients and their families. The committee therefore intends that the seriousness of an illness be given broad consideration, to take into account all of the circumstances involved.

Expanded humanitarian use of devices

The Safe Medical Devices Act of 1990 included a new provision authorizing the use of devices for humanitarian purposes for small populations of targeted patients for whom products are not generally available to treat or cure a condition or disease. This provision permits device approval based on specified safety criteria and exempts effectiveness showings from approval requirements. The provision required the Secretary to issue implementing regulations within 1 year. However, final regulations were not promulgated until June of 1996 and only became effective in October of that year—almost 7 years after the provision became law.

The regulations currently provide for a 45-day designation period and a 180-day review period to show safety (compared with the 30-day period now required to show safety under an investigational device exemption (IDE) and the 180-day period required under a PMA to show safety *and* effectiveness). The legislation would provide for a 60-day period to review the safety showing. This period is greater than that required for a response to an investigational device exemption application, which requires a finding that a device is sufficiently safe for use in humans, but less than the 180-day period required for a showing of safety and effectiveness under a premarket approval application.

The statute currently requires an institutional review board (IRB) to approve use of the product *before* the product may be used. However, because some IRB's typically meet infrequently a patient is at risk of harm or death if the IRB is unable to consider a physician's request. This proposal would permit a physician to approve use of the product where the patient would suffer harm or death waiting for the approval if the physician in good faith is unable to secure IRB consideration but later notifies the IRB.

Finally, current law requires the company to reprove its exemption every 18 months even if there is no basis for doubting the status of the exemption. Further, the program automatically expires after 5 years. This proposal would require the company to reprove its exemption when the Secretary has cause for requiring such showing; and no longer requires a sunset of the program.

TITLE II—INCREASING ACCESS TO EXPERTISE AND RESOURCES

Interagency collaboration and FDA facility consolidation

The legislation requires the Secretary to implement programs and policies that will foster collaboration between the FDA, the Na-

tional Institutes of Health, and other science-based Federal agencies to enhance the scientific expertise available to the Commissioner for the evaluation of emerging medical therapies, including complementary therapies, and advances in nutrition and food science.

The committee includes this provision to help ensure that the FDA has available to it the expertise and assistance it may need to enhance its own capacity for the efficient evaluation of applications for the approval of products that pose substantial new scientific or technical issues.

The committee strongly supports the consolidation of FDA facilities at White Oak, MD, as proposed by the FDA in consultation with the General Services Administration (GSA). The consolidation of FDA's facilities into state-of-the-art laboratory space and supporting office space has great significance not only to the FDA, but to the Nation as a whole.

FDA laboratories and facilities are now scattered among 50 buildings at 20 locations in the Washington, DC, metropolitan area. Many of these facilities are old, poorly maintained, and do not meet accepted standards for laboratory research. These antiquated facilities and fragmentation of agency programs have proven burdensome in many ways. The cost of leasing space for FDA and the difficulty in managing programs that are so widely scattered in the Washington area is a tremendous burden for the FDA. The FDA cannot do its job if it does not have the tools it needs to accomplish its mission. The committee believes that providing the FDA with consolidated, modern, state-of-the-art facilities will enable the FDA to do its job faster and more efficiently, benefiting the taxpayer and the consumer.

Sense of the committee regarding mutual recognition agreements and global harmonization efforts

The U.S. Government has long been involved in negotiation—an effort being spearheaded by the U.S. Trade Representative (USTR)—with representatives of the European Union (EU) Commission to achieve a mutual recognition agreement (MRA). The overall MRA, being directed by Under Secretary for International Trade Stuart Eizenstat and USTR Deputy Trade Representative Jeffrey Lang, has been estimated by the Department of Commerce as a possible savings to United States businesses of $100 million annually. The Commerce Department has also stated that this MRA will expedite $40 billion in transatlantic trade each year between the United States and the 15-nation EU by eliminating trade barriers. The Department of Commerce and the USTR expect this agreement to provide especially strong benefits to the U.S. telecommunications industry, the U.S. medical device industry, and the U.S. pharmaceutical industry.

Only recently have we gotten good news that an important portion of the MRA which involves the *mutual recognition* of inspection reports for good manufacturing practices (GMP) for medical device and pharmaceutical products, and medical device review standards may be close to an agreement. It is important to recognize these efforts for what they are: these agreements would *not* make GMP inspection or product review necessarily uniform but

would allow equivalent regulatory bodies to conduct a single review or inspection that would satisfy all of the criteria for all of the countries concerned, instead of conducting multiple inspections, often at great costs. The committee intends and specifically instructs the FDA to promote and protect the health of the American public in implementing the MRA. The MRA should not place U.S. consumers of drugs and devices at risk, nor adversely affect the quality, quantity, or variety of drugs available to the American public.

This MRA also will lay a flagstone in the path being built toward harmonization activities on things like increased reliance on international standards, an effort the Food and Drug Administration and professional groups are already engaged in with their foreign counterparts. This is an especially important effort in light of the extent to which our marketplace has become globalized.

There was agreement by President Clinton and his European counterparts at last December's U.S.–EU Summit meeting that this MRA represents a critical point that has taken a number of years to reach. The United States was recently urged by President Santer of the European Commission to achieve a successful conclusion of these negotiations, and the committee is pleased to see that the excellent effort coordinated by USTR is close to having positive results.

The committee looks forward to seeing more global partnership in the form of a quality mutual recognition agreement that compliments both our high public health and safety standards in the United States and appropriate international regulatory controls. As noted by Commerce Secretary Richard Daley, "Under this landmark agreement U.S. regulatory agencies for the first time have entered into a cooperative international agreement that strives to reduce regulatory costs while at the same time seeks to expand market access and protect the health and safety of consumers on both sides of the Atlantic."

Contracts for expert review

For many years, the FDA has contracted with outside individuals and organizations to review part or all of product applications or Agency decisions respecting the safety and effectiveness of marketed products. The FDA contracted with the National Academy of Sciences (NAS) to review the effectiveness of all new drugs for which new drug applications were made effective during 1938–62 and with the Federation of American Societies for Experimental Biology (FASEB) to review the safety of all food substances that the Agency had earlier determined to be generally recognized as safe for their intended use in food. The FDA has contracted with individual experts to review aspects of new drug applications and recently contracted with the Mitre Corporation (now incorporated as Mitretek Corporation) to review supplements to new drug applications. Finally, the FDA has developed a pilot program for third-party review of class I and class II medical device submissions, a step beyond traditional Agency contracting out activities.

There are sound reasons for using outside individuals and organizations to review, evaluate, and make conclusions and recommendations to the FDA with respect to applications submitted

to the FDA. In some instances, individuals outside the FDA have unique expertise not available to the agency. In other instances, the FDA's internal resources are inadequate to handle surges in the workload. In still other instances, internal FDA resources must be focused on priority matters and cannot be diverted to more routine matters that become backlogged. The FDA has in the past used outside individuals and organizations for these reasons.

The legislation explicitly authorizes the FDA to contract with outside individuals and organizations with expertise in relevant disciplines to review, evaluate, and make conclusions and recommendations to the FDA on any form of submission made to the agency. Under this legislation, the FDA retains full authority to make any determinations with respect to the classification, approval, or disapproval of any product. Thus, although outside experts will assist and advise the FDA, they cannot commit or make any final decision for the agency. Final action must be a function solely within the power of the FDA. However, the FDA is advised not to arbitrarily or systematically disregard the recommendations of the reviewers it has accredited and qualified or to redo without cause the work completed by such reviewers.

The legislation requires the FDA to use its authority to use outside experts under contract (on a basis other than a "pilot" or "demonstration" basis) whenever the Secretary determines that doing so will improve the timeliness or quality of the review of an application or submission. It is the intent of the committee that improvements to application or submission review may include providing the Secretary with increased scientific or technical expertise necessary to review or evaluate new therapies or technologies. It is not the intent of the committee that the FDA be compelled to use an outside expert when the timeliness of a review would be improved yet the quality of that review would unduly suffer or vice versa. Rater, the FDA should wisely and rationally use this authority as a tool to manage an increasing workload in an era of flat or declining resources available to the Federal government, and bring to bear outside expertise when it is helpful.

Accredited party reviews

In recent years, the FDA has consumed substantially more and more time for the review of medical devices than in past years. For example, FDA's average review time for premarket notification classifications has increased in the years 1990 to 1996 by well over 100 percent (from 82 days to 178 days for a total review time; from 66 days to 137 days for time in the FDA's hands) while the number of applications has generally held steady. In addition, premarket approval times have increased (from 348 to 773 total days, 247 to 606 days in FDA's hands) on average, while submissions in the same 6 year period dropped from 84 to 43 (almost in half). By statute, premarket notification classifications are expected within 90 days and premarket approvals must be granted or denied within 180 days.

Although the agency represents that review times for devices have dropped recently, the agency's current budget justification confirms continued cause for concern. Even given a net resource increase of almost 4 percent, the agency anticipates a 17 percent in-

crease in the backlog of pending PMA applications and a decline in timeliness of final actions on 510(k) premarket notification submissions—from 59 percent within 90 days to only 40 percent. Again, this is in the context of declining numbers of 510(k) submissions and virtually steady PMA applications.

This delay is in part a consequence of the agency's difficulty in maintaining the technological expertise and capability necessary to review applications within the statutory timeframe. Also contributing to this delay is the FDA's management of its resources. The FDA has regularly made this committee and others aware of its desire to have more resources in order to address its inability to review products within the statutory time frame. In past years, Congress has responded with increasing appropriations. However, as resources available to the Federal Government have tightened, the agency and Congress have been pressed to find alternative sources of revenue.

In August 1996, the agency responded by establishing a "third party" pilot program to review a very limited number of device submissions. For reasons discussed below, that pilot has not been useful in providing alternative revenue sources or in gauging the effectiveness of "third party" review. As a result, the committee decided to expand the agency's pilot program to better supplement FDA resources with fees paid by a product sponsor directly to FDA-accredited reviewers and to supplement FDA expertise with that of other public and private parties. Ultimately, the committee believes that this expansion will reduce delays in medical device reviews and improve the technical sophistication of those reviews.

The legislation provides that accredited individuals and organizations with relevant expertise will, at the option of a product sponsor, be used to provide recommendations to the FDA regarding premarket notifications and premarket approval applications. The FDA will then review those recommendations and make a final decision with respect to classification or approval or disapproval of the premarket approval application.

The provision maintains a strong, continued role for the FDA in the device approval process. For example, the FDA alone accredits the pool of qualified private parties to conduct the reviews and selects from that pool two or more accredited parties from whom the product sponsor may select. Although a product sponsor has the option to select an accredited party, it does so only from a list preselected and accredited by the FDA, thus limiting if not eliminating potential "forum shopping" as it does in its current pilot. The FDA also establishes rules protecting the confidentiality and the proprietary nature of information contained in the review. The FDA promulgates the rules to prevent conflict of interest. The FDA has authority to ensure compliance by the accrediting party and has the ability to withdraw or suspend accreditation of parties not in compliance. In short, the FDA will have all necessary control over the individuals and organizations eligible for selection.

The FDA's role is not limited to accredited-party selection. In addition, the Agency retains all of the authority it has under current law to make final product review decisions. This legislation does not authorize any other person or organization outside the agency to make such a final decision. The FDA will have no less than 30

days (of the 90 days allotted under the statute) to review a submission under section 510(k) and 60 days (of 180 days under statute) to review a premarket approval application. Again, the agency is not bound by an accredited party's determination—there is no presumption given to the accredited party's recommendation of approvability or classification of a product.

The provision expands the types of device submissions that may be considered under the current agency pilot program. The current program is open to nonexempt class I devices and a limited number (approximately 30 at this time) of class II devices. However, because of the limited scope of the pilot fewer than 10 submissions have been considered under the pilot in the initial 10 months of its planned 24-month existence. S. 830 would permit any 510(k) device into the program with several exceptions: specifically, devices that are life-supporting, life-sustaining, or intended for implantation for a period of over 1 year. However, the agency retains discretion to allow these devices to be reviewed by a third party.

As a supplement to the resources available to the FDA, the product sponsor will directly contract with and pay the accredited party at the sponsor's own expense. This mechanism is similar to that proposed by the FDA in its own pilot project at the Center for Devices and Radiological Health. As with the current pilot, the agency retains the ability to review invoices and fee schedules, and, if the agency has cause to believe that a party is engaged in forum shopping or if the submission presents some form of conflict of interest, the agency may review the terms of compensation prior to a particular review. The committee is aware that the Agency does not consider it a worthwhile or reasonable use of resources generally to preapprove or prereview compensation agreements.

The agency's current pilot is clearly not sufficient to permit meaningfully evaluation of a program incorporating accredited-party reviewers. In large part, this is a result of the agency's insistence that no product be reviewed without a vertical standard or guidance document. While for some reviews this may be useful, for most reviews the committee believes that the agency has unwisely consumed resources in developing documents that its own employees have not been required to use for their own product reviews. In addition, the agency has accredited parties that it has certified as capable of preforming reviews, yet only allows them to do little more than follow a cookbook recipe for approval; and again, the agency does not subject its own reviewers to these constraints. Ultimately, through this policy, the agency has unreasonably constrained the scope of the pilot and rendered the pilot virtually without utility. Accordingly, the committee directs the agency, under the expanded pilot program, not to continue this practice except in the limited cases where it is essential to protect the public health. The expansion established under this provision will be subject to independent study within 5 years of the agency's establishing an expanded pilot program with sufficient eligible products or within 4 years of the agency's expanding the program so that 35 percent of products are actually reviewed under the program. A full analysis of the strengths and weaknesses of the program will be conducted and provided to Congress and the public, enabling Congress to extend, modify, or discontinue the program at that time.

Device performance standards

Long before the enactment of the Medical Device Amendments of 1976, voluntary standards-setting organization in the United States and abroad have established performance standards for categories and characteristics related to medical device products. These organizations include the American National Standards Institute (ANSI), the International Standards Organization (ISO), and the International Electrotechnical Commission (IEC), as well as others. Although standards from these organizations are recognized as authoritative, and are therefore followed throughout the world, the FDA has failed to establish any policy regarding their recognition and use under the Federal Food, Drug, and Cosmetic Act in this country. This legislation remedies that problem

The legislation gives the FDA authority to recognize all or portions of appropriate medical device performance standards developed by organizations such as ANSI, ISO, IEC, and any other standards-setting organization. It is the intent of the committee that FDA can reduce the amount of effort required on its part to assess product applications and submissions which show conformity with a standard, recognized by FDA, as the basis for all or part of a product application or submission.

The legislation establishes procedures for recognition by the agency of these standards, grants express authority to FDA to subsequently withdraw a recognized standard, and clearly establishes the FDA's authority to assure that devices that purport or are represented to be in conformance with a standard in fact meet the requirements of the standard identified with the device.

It is important that all medical device performance standards recognized by the FDA under this new procedure be publicly listed, so that any interested person will know the regulatory status of the standard. Accordingly, the legislation requires FDA to public in the Federal Register the name of all standards to which recognition has been given. Any standard not on the published list would not be accepted as recognized by the FDA under this provision.

Other provisions in the Federal Food, Drug, and Cosmetic Act authorize FDA to promulgate performance standards for medical devices using the procedures set forth in the law. This legislation does not in any way change the authority of FDA to promulgate such standards, which may differ from the standards established by certified organizations and recognized under this new provision.

The FDA may not require conformity with any recognized standard as a condition for approving or classifying any type of medical device premarket submission if the submitter demonstrates with information other than that required by a recognized standard that the device is substantially equivalent to a legally marketed predicate device or otherwise provides reasonable assurance of safety and effectiveness.

Importantly, reliance on a recognized standard in a premarket notification, a section 604 classification, or a premarket approval application, will not create a continuing compliance requirement such that legal modifications to devices may not be made. For example, a device classified into class II under section 604, subject to a special control performance standard, may be legally modified without maintaining compliance with the recognized standard, and

without filing a 510(k) submission, if the modification insignificantly affects safety or effectiveness. On the other hand, if the 510(k) were required, the person submitting the premarket notification could choose to rely on the standard or demonstrate substantial equivalence in another way.

The committee notes that the amendment to section 501(e) is intended to ensure that statements or actions directed to the consuming public indicating conformance to a recognized standard must be correct. If they are not, the device will be considered adulterated. Additionally, section 301 is amended to create as prohibited acts false declarations of conformity to a recognized standard or the withholding of information required to be provided to the Secretary under this provision.

Although most national and international standards development organizations use a consensus based approach that allows interested parties to participate in the development of performance standards, the committee recognizes the importance of public participation in agency decision making. Therefore, the committee is recommending that the FDA provide the public an opportunity to comment on agency decisions to recognize standards on a case-by-case basis when a particular standard may warrant or benefit from further public comment. The committee is not recommending that the Agency use notice and comment rulemaking to recognize these standards because their use by industry is voluntary. Instead, the committee is recommending that the agency, as appropriate, provide the public a reasonable opportunity to comment in a way that is consistent with the agency's recently issued Good Guidance Practices.

TITLE III—IMPROVING COLLABORATION AND COMMUNICATIONS

Collaborative determinations of device data requirements

The committee is aware that persons who submit premarket approval applications and the FDA not infrequently disagree on what constitutes an appropriate showing of device effectiveness. Significantly, and unfortunately, this conflict at times emerges well into the review process, when it may be too late to remedy. Although the agency has been willing to meet with persons who intend to submit investigational device exemption applications, the committee believes that a special meeting to determine the scientific showing for device effectiveness is necessary and will prove to be an investment against the significant costs to companies and the FDA related to review process conflicts over device effectiveness showings. The vehicle for obtaining a meeting to determine the type of valid scientific evidence necessary to demonstrate effectiveness will be a written request which sets forth a full device description, a detailed description of the conditions of use and, when available, information about the device's expected performance. Within 30 days of the meeting, FDA will provide its written response identifying the types of evidence that will demonstrate effectiveness for a specified device for a particular use.

The committee intends that FDA will be found by its determination of device effectiveness requirements, unless holding the agency to its determination is contrary to the public health or, based on

new information, the determination is scientifically inappropriate. Importantly, "new information" may not include a re-examination of the information before the FDA when the agency made its determination of types of scientific evidence needed to show effectiveness. In other words, when public health protection requires a change in direction, the committee intends that such change will occur. However, this provision is intended to establish an institutional commitment within the FDA to stand by its advice regarding appropriate scientific showings and to thoroughly consider the implications of such advice, when given.

The intent of this provision is to be a starting point for designing an investigational plan; it should only result in a specification of the *types of valid scientific evidence* that will demonstrate effectiveness. The provision is not intended to address the development of a complete device investigational plan.

This amendment of section 513(a)(3) is also intended to carry through the philosophy of the "Medical Device Amendments of 1976." Those amendments were committed to avoiding overregulation of devices. Section 301 achieves this laudable goal by requiring that the FDA's specification of the types of evidence to demonstrate a reasonable assurance of effectiveness "result [from] a determination by the [Agency] that such data are necessary to establish device effectiveness and that no other less burdensome means of evaluation device effectiveness is available which would have a reasonable likelihood of resulting in an approval." Simply put, the FDA may not ask for the ultimate study to prove effectiveness. It must ask for the least burdensome type of valid scientific evidence that will meet Congress' criteria for effectiveness. It is Congress' formulation for proving effectiveness that counts. FDA has never had freedom to require evidentiary showings that exceed what is required under the law for an approval. This provision reinforces that fact.

Collaborative review process

Consistent with a purpose behind section 310, the committee intends that section 302 facilitate communications between FDA and persons who submit premarket approval applications to improve the efficiency of the device review process. Because the committee is aware that the FDA has failed to timely review PMA's, this bill includes a provision requiring a 180-day review that cannot be extended or modified by the agency's request for an amendment of the PMA. Instead, when the agency desires additional information, the regulatory review clock will stop until the applicant responds to the agency's request, including a response that the applicant will rest on its application as is. The committee intends that the 100 day meeting required by section 302 will occur a bit after the midpoint in the 180-day review process and will reinforce the 180 day review deadline by requiring the FDA to identify the deficiencies that would preclude an approval of the PMA.

This requirement will force the agency to critically consider the PMA up front in the review circle and not wait until late in the review process, which has all too often been the agency's pattern. Additionally, the section will require FDA to describe the information necessary to bring the PMA into an approval form, a form in

which the FDA would be prepared to approve the pending PMA if certain tasks, excluding clinical investigations, were outstanding and reasonably capable of being accomplished within a reasonably short period of time. Both the statement of deficiencies and advice to improve the PMA are to be in writing and made available to the applicant prior to the meeting. Importantly, any deficiency discovered by the agency after the 100-day meeting, must be reduced to writing by the Agency and *immediately* provided to the applicant. For purposes of this provision "immediately" shall mean within 48 hours of an agency employee becoming aware of the deficiency.

TITLE IV—IMPROVING CERTAINTY AND CLARITY OF RULES

Policy statements

In the past decade, the FDA has relied less on developing its policies and procedures through formal, public, or binding mechanisms such as promulgating regulations and more on the use of informal policy statements, including guidelines, points to consider, and memoranda, generally without the benefit of public comment. This has had the advantage of consuming fewer agency resources than the cumbersome process of promulgating substantive regulations and permits the agency to respond more quickly and efficiently to requests for policy guidance.

However, the FDA's increasing reliance on policy statements has also produced several problems. First, until recently, the FDA has maintained no compilation of these documents. The regulated industries and the public were often not aware that they existed or did not know how they could be found. Second, until recently, there was no systematic process for their adoption or amendment. There may or may not have been an opportunity for interested outside individuals and organizations to have any input into their formulation or amendment. Third, there was inconsistency among FDA personnel in the use of these documents. Some FDA employees insisted that industry strictly follow them, and others did not.

In February 1997, FDA published in the Federal Register (62 Fed. Reg. 8961) the Good Guidance Practices document identifying policies for the development, issuance, and use of guidance documents. The committee recognizes that this new policy on guidance has only been effective for a short time and that it is premature for the Congress to require FDA to promulgate this new policy as a regulation without adequate time to assess the success of this policy and consider modifications, if any, that should be made to the policy. However, it is the committee's intent that ultimately, the policies governing guidance documents and informal policies be in regulation. Therefore, the legislation requires that FDA promulgate a regulation specifying the policies and procedures of the FDA for the development, issuance, and use of guidance documents by February 27, 1999.

Product classification

It is often difficult for an applicant to determine the proper classification of a product as a drug, biological product, or device. Even where the classification of the product is known, the proper organizational center in the FDA where the application will be handled

can be uncertain. The legislation therefore provides that, within 60 days of receipt of a written request, the FDA must provide an applicant with a written determination regarding the classification of the product or the component of FDA within which it will be handled, or both. This determination is binding. If the FDA fails to meet this requirement, the applicant's designation shall be final and binding. However, the FDA is given authority to modify these otherwise binding determinations and designations for public health reasons.

Use of data relating to premarket approval

The committee recognizes that in some instances minor differences between separate versions of the same device can result in significant divergent performance characteristics and clinical results. Therefore, the FDA may find under Section 403 of S. 830 that on occasion it may not be scientifically appropriate to utilize data from a single (or even a multiple) application to approve another device, determine whether a product development protocol has been completed for another device, or establish a performance standard or special control for another device.

Labeling claims for medical devices

With the "Medical Device Amendments of 1976," Congress intended that device classification and approval decisions be made based on the intended use of devices as described in labeling. Over the years, FDA has made premarket regulatory decisions based on uses for devices that are unrelated to the intended uses set forth in labeling. This section includes two provisions that express the committee's specific intention to limit FDA's review of premarket submissions to the proposed labeling before the agency. Considerations like cost effectiveness, relative effectiveness, or whether the product effects some improvement in a patient's "quality of life," are irrelevant to a premarket review unless such claims are included in proposed labeling. Simply put, the committee does not want FDA to exceed its jurisdictional responsibilities by incorporating into the review process claims not before the agency for review consideration.

For premarket notification submissions, the labeling proposed in the submission will be controlling of a device's intended use. If the intended use is the same or sufficiently similar to the intended use of a predicate device, then the device may be found to be substantially equivalent to the predicate. No considerations outside of the proposed labeling for the 510(k) device should bear on the question of whether or not the proposed labeling of the newer device is compatible with the labeling of the predicate device.

For premarket approval applications, the determination of whether or not there is a reasonable assurance of device safety and effectiveness must be based on claims in proposed labeling if such labeling is neither false nor misleading. The FDA may fairly consider all facts which are pertinent to proposed labeling in PMS's in determining whether or not the labeling is false or misleading. Facts which are "pertinent" to proposed labeling are those which directly relate to claims in such labeling. For example, proposed labeling stating that a device is for use in treating atherosclerosis

cannot be false or misleading because another device is more effective for that purpose. Nor can the proposed labeling be false or misleading because another device provides the same treatment benefits but is less expensive to purchase and operate. However, the failure to state a material fact about the device itself will make labeling in a pending PMA false or misleading.

Definition of a day

The committee has included in this legislation the codification of FDA's method of calculating a day, as that term is used in various places in the Act in which specified times for the FDA to complete statutory product review requirements are identified. The committee believes it is important to have a consistent understanding of a day both as a means for persons who make submissions to FDA to determine where in the review cycle their submission resides and to make FDA more accountable for the timeliness of its reviews. Concern has been expressed that FDA performance data are difficult to review because often it is difficult to determine what is being presented by the FDA for analysis. The committee hopes defining a day for product reviews will help lessen the difficulty experienced in evaluating FDA performance data.

For purposes of determining the length of review of various specified product submissions, a "day" will be a calendar day in which the agency has responsibility to review a submission. The regulatory clock will not commence until the date a complete submission is received by the FDA. When the agency reviews a submission and requests additional information, the regulatory clock will stop on the date that such a request by FDA is made. The clock will re-commence when the additional information is received by the FDA or when the regulated person requests that the review continue.

Certainty of review timeframes

In section 406, the committee set a timeframe for reviewing premarket notifications required under section 510(k). Also, a strict limit was placed on the 180 day requirement for PMA reviews.

Historically, FDA has operated as if premarket notification classification determinations were required to be made in 90 days. Indeed, the internal yardstick for success in reviewing these submission was the 90-day timeframe. The committee believes that to ensure accountability, and avoid the long review times seen from 1993 through 1996 for a majority of devices, it is important to codify this informal agency yardstick. This change in the Act should not create any disadvantage or hardship for the FDA because it does no more than put into law FDA's longstanding practice. Finally, with regard to the review time for PMA's, the legislation clearly states the committee's intent that FDA should approve or disapprove a PMA application within the 180-day timeframe set in the Act. The committee recognizes that this may result in the disapproval of PMA's that FDA today might continue to work on beyond the 180-day period in the well-intentioned effort of ultimately approving the PMA.

Limitations on initial classification determinations

The committee included section 407 in S. 830 because of a concern that FDA was inappropriately using the device premarket notification process for compliance purposes and not solely for its intended purpose of classifying devices intended for introduction into interstate commerce after May 28, 1976, the enactment date of the "Medical Device Amendments of 1976." Over the past five years, the FDA has withheld device classification determinations of substantial equivalence because of its belief that firms were not in compliance with good manufacturing practices. Such firms were placed on a "reference list" and were not removed from the list until FDA was satisfied that such firms' facilities complied with GMPs. Once a reference list form satisfied FDA with its GMP program, the agency would complete a pending premarket notification review and device classifications would then occur.

This process was unfair and denied device manufacturers an opportunity to dispute effectively FDA's allegations that firms were not in GMP compliance. FDA set itself up as judge and jury and, in essence, administratively enjoined the classification of devices until manufacturers satisfied the agency's view, notwithstanding a regulated person's disagreement with FDA.

Clearly, FDA has substantial authority to enforce the Act against illegal devices and the persons who market them. It is unacceptable that the agency misuse premarket notification to avoid enforcing the Act. FDA can find a device substantially equivalent to a predicate device and still inform the device manufacturer that although the device is substantially equivalent it should not be marketed because of the agency's view that the device does not comply with the law in some specified respect. Then, if a person markets the device after such notice, FDA can enforce the Act. This approach was used by FDA for years before the advent of the reference list.

Although the FDA announced some time ago that it had discontinued its reference list program, the committee is aware that the agency still has withheld premarket notification determinations for devices because of the agency's unilateral determination of a lack of GMP compliance. Accordingly, the committee believes this provision is essential to once and for all eliminate all reference-list-like programs. Simply put, initial classification determinations may not be withheld for any compliance-related reason under the Act, including any purported violation of GMPs.

Clarification with respect to a general use and specific use of a device

Section 408 of the bill represents the committee's interest in clarifying when devices with general intended use labeling may be predicates for substantially equivalence determinations for newer devices with more specific intended use statements. This clarification is important because FDA has not established a consistent pattern upon which persons who submit premarket notification may rely.

To be substantially equivalent to a legally marketed device, a person intending to market a device must show, among other things, that a newer device has the same, or nearly the same, in-

tended use as a legally marketed device. Some legally marketed devices, which are labeled for general uses, have been used as predicate devices for substantial equivalence determinations regarding newer devices with more specific claims, *e.g.,* condoms labeled for prevention of sexually transmitted diseases were predicates for condoms labeled for HIV prevention. Here, FDA found that the condom labeled for a general use could be a predicate for a condom labeled for prevention of a specific sexually transmitted virus, HIV.

This determination made perfect public health sense, despite the fact that the general use labeling pre-dated the "Medical Device Amendments of 1976" and HIV was unknown at that time. Consequently, the specific use for HIV prevention could not have been included within the general use labeling for condoms. The committee's concern is that although the agency can make good determinations like the one just discussed, no policy exists regarding the availability of general use predicates for regulated persons to rely upon.

The committee believes that FDA should state its policy regarding reliance on general use predicates in the context of a regulation. The regulation should state when reliance on a general use predicate is appropriate. FDA should permit premarket notification submitters to provide information showing that specific uses for a device are reasonably included within a predicate's general use. For example, if the medical literature shows that a newer device is used for several specific uses within a predicate's general use, then FDA should permit the general use predicate to be the basis for a substantial equivalence finding for the newer device. The FDA's regulation should seek to describe rules that the agency and industry can follow.

Clarification of the number of required clinical investigations for approval

The drug amendments of 1962 added to the Federal Food, Drug and Cosmetic Act the requirement that the effectiveness of a drug be established by "substantial evidence," which is defined as adequate and well-controlled investigations, including clinical investigations, by qualified experts on the basis of which such experts could fairly and responsibly conclude that the drug will have the labeled effect.

The committee believes that the science and practice of drug development and clinical evaluation have evolved significantly in the past 35 years, and this evolution has implications for the amount and type of data needed to support effectiveness in certain cases. Modern clinical trial design often utilizes multiple investigators, multiple study sites, randomization, large enrollment numbers, statistical power, controls, clinical endpoints and other mechanisms that can demonstrate the reproducibility underlying FDA's request for two or more separate studies for each new drug and/or indication. Therefore, it is the committee's understanding that independent substantiation is the scientific basis underlying FDA's substantial evidence requirements.

The FDA usually interprets the requirement to demonstrate substantial evidence of effectiveness to require two adequate and well-controlled clinical studies, but has shown flexibility and approved

some drugs on the basis of one adequate and well-controlled clinical study. Given scientific advancement in the past 35 years and the promise of further advancement, it is the committee's belief that the structure of a particular clinical protocol and the quality of the data underlying a new drug application should guide FDA's substantiation requirements. Therefore, the legislation confirms the current FDA interpretation that substantial evidence may, as appropriate, when the Secretary determines, based on relevant science, consist of data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained either before or after the investigation).

The statutory standard for proof of effectiveness of a medical device was purposely chosen in the Medical Device Amendments of 1976 to be different from that for new drugs. Different language was used for the express purpose of emphasizing this difference. As the Cooper Committee emphasized in its 1969 report, drugs and devices are different in nature and present different issues when considering safety and effectiveness. For medical devices, for example, the skill of the person using the device is often of paramount importance, in contrast with the use of new drugs.

The committee amended section 513(a)(3)(A) of the Act to permit effectiveness to be demonstrated with "one or more well-controlled clinical investigations." This requirement replaces the one in current law which literally requires more than one well-controlled clinical investigation to demonstrate a reasonable assurance of device effectiveness. The committee changed the law because FDA has typically required only one well-controlled clinical investigation to demonstrate device effectiveness and it makes little sense to continue a law in a manner inconsistent with its interpretation by an expert, scientific agency.

TITLE V—IMPROVING ACCOUNTABILITY

The committee recognizes the ongoing effort at FDA to improve its performance in meeting the statutory deadlines and other responsibilities imposed upon the FDA under the Federal Food, Drug and Cosmetic Act. The Prescription Drug User Fee Act has assisted the FDA in coming closer to meeting the statutory review times established in the Act. The recent efforts by the Center for Devices and Radiological Health to reduce the 510(k) backlog, more prompt review of Investigational Device Exemptions, and the pending Center for Devices and Radiological Health (CDRH) re-engineering effort are all promising signs of a new attitude and responsiveness at the FDA. Nonetheless, the committee remains concerned that there are no effective measures available to ensure FDA compliance with statutorily required performance goals.

The legislation requires FDA to develop an agency plan to come into compliance with the Act and provide an annual report providing detailed information regarding implementation of the agency plan, including statistical information which will assist the committee in fulfilling its oversight responsibilities.

Notwithstanding the efforts by the agency noted above, the committee remains concerned that review times for many products are substantially in excess of those required in the FFDCA. Further, the agency is in many cases behind in its reporting requirements

and is incompletely implementing other requirements. An example of the latter are the regulations promulgated by the Health Care Financing Administration following enactment of the Clinical Laboratory Improvement Amendments of 1988 (CLIA).

Under CLIA, the FDA was provided the responsibility to categorize the complexity of new in vitro diagnostic (IVD) devices. However, the FDA failed to undertake this task and the responsibility for regulating the complexity of these IVD products was assumed by the Centers for Disease Control and Prevention (CDC). At the same time, FDA continues to conduct extensive evaluations of these IVD devices before clearing them for market under the FDCA, including reviewing their instructions for use.

The committee is concerned that this dual responsibility has resulted in a process that causes confusion and unnecessary conflict for IVD device manufacturers. In many cases, this overlap has delayed the delivery of potentially lifesaving devices to market. Additionally, CDC's focus on the same safety and effectiveness issues as FDA highlights the wastefulness of this duplicative review. Therefore, the committee believes that FDA should reassert its exclusive role in the implementation of the complexity evaluations under the CLIA regulations.

TITLE VI—BETTER ALLOCATION OF RESOURCES SETTING PRIORITIES

Minor modifications

In section 601, the committee addressed changes made in investigational devices and modifications of approved PMA devices. First, the committee requires the FDA to promulgate a regulation modifying its current investigational device exemption regulation by including a provision that permits developmental changes to investigational devices that are based on information learned during an investigation without submitting a supplement to an approved investigational device exemption application. Specifically, if a study sponsor determines, based on credible information, that the change does not affect the scientific soundness of the investigational plan or patient rights, and the change does not constitute a significant design change or a change in basic operating principles, then no supplement of original IDE application will be necessary. For purposes of this provision, "credible information" shall mean information upon which a reasonable person in a manufacturer's position would rely upon in making a decision to change or modify an investigational device.

The committee also altered section 515 of the Act to accommodate this amendment of the FDA's investigational device exemption regulations. In addition to permitting the use in PMA's of data from devices altered during an investigation, the agency will be required to consider data from approved device investigations for devices already subject to PMA approvals, when the data are relevant to the design and intended use of the device subject to the pending PMA. In other words, if PMA data for a device are available for use by an applicant, that data could be used to approve a newer version of an already approved device if other data address any differences between the approved device and the one pending before the agency.

The committee looked at two forms of change to an approved PMA device: Manufacturing changes and incremental device design changes. In lieu of a supplement for a manufacturing change, the bill requires that manufacturers proposing such a change provide the FDA a 14-day notice prior to commercial distribution of a device manufactured under the changed conditions. The notice must provide a detailed description of the change, data or information supporting the change, and an assertion that the change was made under Good Manufacturing Practices (GMP's). The committee believes that the agency's new GMP regulation, including its design validation provisions which address all changes that could affect device performance, provides adequate protection for the public health in lieu of supplements to the approved application. This is particularly true in light of the fact that the agency approves manufacturing facilities as part of PMA product approvals. Avoiding delays in implementing manufacturing changes cuts costs and typically results in improved products. Importantly, with the notice required under this section, FDA could dispatch inspectors to review the changes that require attention. Moreover, if a change appeared suspect based on the notice, administratively FDA could stop shipments of devices made under the changed conditions. All in all the purpose of this provision is to avoid delay and reduce the use of FDA resources on issues that should not merit the agency's attention.

The committee addressed incremental design changes to approved PMA devices that affect safety or effectiveness by requiring the FDA to approve a supplement if bench data demonstrate that the design modification achieved its purpose and clinical data from the approved application and supplements thereto demonstrate a reasonable assurance of safety and effectiveness for the modified device. However, if the Secretary believes that additional clinical data are necessary, the Secretary may require such data but only insofar as the data relate to the design modification.

This change reflects the committee's understanding that devices develop incrementally, often through very small modifications. To avoid over regulation and wasteful expenditure of agency review resources, the committee wants the Agency to determine when new clinical data are necessary as opposed to presuming such data are always necessary.

Environmental impact review

The National Environmental Policy Act requires that all Federal action be subject to environmental consideration. Some State laws also require a similar analysis. In only one instance, however, has the FDA ever determined that action on a new drug application might potentially have a significant environmental impact. Even in that instance, the importance of the drug involved to human health outweighed the environmental impact and the drug was therefore approved. In the meantime, new product sponsors are generally required to file environmental assessments with new product approval applications, adding substantially to the cost of new product development, adding time to the development and approval process, and consuming valuable FDA review resources.

The legislation ends the automatic requirement for filing environmental assessments, environmental impact statements, or other environmental considerations. New product sponsors would be required to conduct such assessments only if the FDA in writing and specifying the basis therefore, determines that there is a reasonable probability that the environmental impact of the action is sufficiently substantial and within the factors that the FDA is authorized to consider under the Federal Food, Drug, and Cosmetic Act and that consideration of that impact will directly affect the decision on the matter. This assures that, whenever environmental considerations are in fact significant, they will be fully analyzed and taken into account and that industry and agency resources will be focused on considering issues related to the safety and effectiveness of products.

Exemption of certain class devices from premarket notification requirements

Under the medical device provisions of the law that were enacted as part of the Medical Device Amendments of 1976 and amended under the Safe Medical Devices Act of 1990, approximately 97 percent of all devices were cleared for marketing through FDA's premarket notification program. When a device is found to be substantially equivalent to a legally marketed device, it may be marketed after the FDA issues an order making that finding.

After the enactment of the Safe Medical Devices Act of 1990, severe backlogs of premarket notifications and premarket approval applications developed at the FDA. Recognizing that part of the problem was the sheer number of notifications the agency was receiving for class I or II products that posed little risk, President Clinton announced a reinventing government initiative to eliminate the notification requirement for some devices posing a minimal risk, and the FDA has now acted to exempt a substantial number of such devices. By eliminating premarket notification reviews for some low-risk devices, agency resources could instead be used on more critical devices, including those subject to premarket approval applications.

Building on the President's initiative, the legislation exempts all class I devices from premarket notification requirements, except those the intended use of which is of substantial importance in preventing impairment of human health, or presents a potential unreasonable risk of illness or injury. In addition, the FDA is required to review all class II products to determine those that should and should not be exempt from the section 510(k) process. The FDA is provided 30 days to complete the class II exemption process.

Because the agency on its own initiative has already had this matter under review for several years, and because the committee put the agency on notice through multiple requests over the last year for a list of any such devices which do not require premarket notification to protect the public health, this is a reasonable time within which to complete the job.

Further, at any time, on the Secretary's own initiative or in response to the petition of an interested person, the FDA may exempt a type of class II device from the section 510(k) process. By

eliminating low-risk devices from the FDA's premarket review responsibility, FDA personnel will be better able to handle within statutory deadlines the remaining section 510(k) notifications and premarket approval applications for devices that may pose a risk to public health and safety or provide health benefits to patients.

Evaluation of automatic class III designation

Section 604 includes a process that permits the Secretary to classify devices based on the Act's risk-based classification criteria when a device is found to be not substantially equivalent to a predicate device. Specifically, thirty days after receipt of a not substantially equivalent determination, the person receiving the Secretary's classification order may request that the Secretary make a risk based classification determination for the person's device, if the type of device had not been previously classified. The manufacturer should provide information to assist the Secretary in making the risk-based classification. The Secretary will then determine the device's classification based on the classification definitions in section 513(a)(1). These definitions have been used by the Secretary to classify or reclassify over a thousand types of devices.

Within 60 days of the above request, the Secretary must make a classification determination, placing the device into one of three statutory device classes. If the device is placed into classes I or II, it may be commercially distributed immediately. Of course, like any device, devices classified into class I or II under section 604 will be subject to all provisions of the Act. However, if the device is placed in class III, its status will remain unchanged from its not substantially equivalent designation; that is, the device will be classified into class III and will require an approved premarket application under section 515 before marketing.

A device may be placed into class II conditioned upon complying with "special controls." Devices placed into class II under section 604 must comply with those controls to maintain a class II status. A failure to comply with special controls will result in the device reverting to its not substantially equivalent, class III designation. Marketing of a class III device under these circumstances will result in the device being adulterated within the meaning of 501(f)(1)(B), assuming it has not been distributed under an investigational device exemption, because the device will be an unapproved class III device classified under section 513(f)(1).

Once a device is classified into class I or II under section 604, it becomes a predicate for future premarket notification submissions. Persons who file reports under section 510(k) may demonstrate the substantial equivalence of newer devices to these predicates. Substantial equivalence may be demonstrated by complying with the specified special controls used to establish the classification of the predicate device and other information, when necessary, or it may be demonstrated in another manner. As with current law, the person making a premarket notification submission will have the option of determining how to demonstrate the substantial equivalence of a device to a predicate device, and the agency will have the responsibility to make substantial equivalence determinations.

The committee realizes that "special controls" can be controls or a variety of controls that will assist in providing a reasonable assurance of device safety and effectiveness. When conducting a classification review under this section, the Secretary may classify a device into class II even when special controls to not yet exist. Under these circumstances, the Secretary should inform the person seeking a risk based classification of the Secretary's intention to rely on a special control in the future and specify the nature of the special control.

Importantly, the fact that a device is subject to a special control under this section does not mean that enforcement authority over in other parts of the Act become ineffective. For example, postmarket surveillance and labeling can be special controls. Nonetheless, postmarket surveillance is still enforceable as a misbranding under section 502(t) and specified labeling instructions remain enforceable under either section 502(a) or 502(f)(1) as misbrandings, depending on the labeling control at issue.

The committee included section 604 to avoid the needless expenditure of the Secretary's resources that would occur if lower risk devices were subjected to premarket approval reviews under section 515 because such devices were unique and found to be not substantially equivalent to a predicate device. The Committee also believes that section 604 may permit the Secretary to avoid time and resources consuming substantial equivalence determinations that rely on remote predicates. The Committee did not include this section in its bill to increase significantly the number of not substantially equivalent determinations, and specifically it did not intend that section 604 would otherwise alter the Act's substantial equivalence provisions or the Secretary's longstanding approach to the 510(k) classification process.

Concern has been expressed that the Secretary will attempt to use this provision as a means of creating mandatory [. . . requirements] out of voluntary ones, thus subjecting regulated persons to enforcement consequences without process. That is not the Committee's intent. For example, once a device is classified into class II under a risk based assessment, compliance with applicable special controls will be unnecessary to demonstrate substantial equivalence between a newer device and the section 604 predicate device, unless the special control is a part of the device's intended use. The Committee's intent behind section 604 is simple: Section 604 will permit the Secretary to avoid over-regulation of devices that should not be subject to premarket approval requirements. In other words, the Committee does not intend section 604 to supplant or otherwise change the "510(k) classification process."

Tracking

The Safe Medical Devices Act of 1990 added a new provision to require device tracking for every device the failure of which would be reasonably likely to have serious adverse health consequences and which is a permanently implanted device or a life-sustaining device that is used outside a device user facility, as well as any other device designated by the FDA.

This statutory mandate has proven to be uncertain with regard to which devices require mandatory tracking. The FDA's regulation

for tracking identifies an illustrative list of devices subject to mandatory tracking, suggesting that the list is comprehensive, yet not complete.

To address these problems, the legislation requires FDA to affirmatively list those devices which it intends to be subject to tracking. Devices not so listed are presumed exempt from tracking requirements until such time as FDA chooses to affirmatively require tracking. The legislation does not modify the existing mandatory or discretionary tracking authority. The Committee notes the intent of the tracking provisions in the Safe Medical Devices Act of 1990 was to track medical devices to facilitate recalls.

Postmarket surveillance

The Safe Medical Devices Act of 1990 also included a provision requiring a manufacturer to conduct postmarket surveillance for any device first marketed after January 1, 1991, that is a permanent implant the failure of which may cause serious adverse health consequences or death, is intended for use in supporting or sustaining human life, or potentially presents a serious risk to human health. In addition to this mandatory surveillance, FDA was authorized to require postmarket surveillance for any device when the agency determined that surveillance is necessary to protect the public health or to provide safety or effectiveness data. All manufacturers subject to mandatory postmarket surveillance were required to submit protocols for FDA approval within 30 days of first marketing the device. The FDA was required to determine the adequacy of the principal investigator and the protocol and to approve the protocol after review by an appropriately qualified advisory committee.

In practice, the provision for mandatory surveillance, like the one for mandatory tracking, is so broadly worded that it is causing a good deal of uncertainty about those devices which are subject to this requirement. Further, the committee is concerned that FDA not interpret the postmarket surveillance authority as power to require longitudinal studies for FDA approved products. The committee legislation repeals mandatory surveillance and provides the Secretary with broad discretion to implement postmarket surveillance. Under current law, required surveillance is limited to devices first introduced into commerce after January 1, 1991. Under the legislation, subject to the Secretary's discretion, any device may be subject to surveillance.

The legislation sets the initial period of surveillance at 24 months. After an informal hearing to consider the need for further surveillance, FDA may require that the surveillance continue for such time as is necessary.

Since 1976, and reinforced in 1990, the Federal Food, Drug, and Cosmetic Act has required medical device reporting by distributors as well as manufacturers. The Safe Medical Devices Act of 1990 added this requirement for device user facilities. As a result, there has been a substantial increase in reporting for medical devices, including, as documented by the GAO, much duplication and some inaccurate filings. Further, the FDA, after request by the committee, has been unable to confirm that it either tracks distributor reports or acts on the basis of such reports. To avoid duplication and

the costs associated with it, the legislation continues to require manufacturers and user facilities to report adverse events to the FDA but eliminates distributor reporting. Because user facilities and manufacturers submit medical device reports to the FDA, there is no need for additional reporting by distributors. Further, the registration requirement for distributors is deleted. Finally, the record keeping requirements for distributors are retained. Because the agency has represented it is aggressively pursuing reforms to address the concerns raised in the GAO report with respect to user reporting, namely, letting a contract to explore a sentinel, statistically significant user reporting system, the committee has not proposed a statutory remedy in that area at this time.

Pilot and small-scale manufacture

An important part of applications for new drugs and biological products consists of the information on chemistry, manufacturing, and controls (CMC). During the investigation of a new product, only a relatively small amount of the drug is needed to support the preclinical and clinical trials. It is only after marketing approval is obtained from the FDA that large-scale manufacturing is justified.

For some drugs, where the evidence of effectiveness is overwhelming, companies are prepared to scale up to large manufacturing facilities even before FDA approval is obtained. For small companies with modest capitalization, however, it is common practice to wait for FDA approval of the premarket approval application before scaling up to larger processes. This is particularly characteristic of startup biotechnology companies.

In the past, the FDA has for some drugs required CMC data relating to large-scale manufacture before approval will be granted. This penalizes small companies and especially the biotechnology industry. The legislation therefore states the general rule that the FDA review and approve new drugs and biological products on the basis of pilot and small-scale manufacturing, and permit the company to scale up to a larger facility after the product has been approved. Scaling up can readily be undertaken on the basis of process validation, without additional clinical trials. Only in the very rare case where full-scale production is necessary to ensure the safety or effectiveness of the new drug or biological product prior to approval is the FDA given the authority to require such manufacture as a condition of approval. This is the approach that has been announced in the Reinventing Government initiative relating to drug and medical device regulations. The need for supplemental approval of the manufacturing changes needed to scale up to larger facilities is subject to the new requirements in section 614 of the legislation.

Requirements for radiopharmaceuticals

The purpose of section 610 is to acknowledge the special characteristics of radiopharmaceuticals used for diagnostic and monitoring purposes that should be taken into account in evaluating their safety and efficacy. Radiopharmaceutical diagnostic and imaging agents are not normally used chronically. They are administered on an occasional and intermittent basis. Because of the contribution of the radioactive isotope, only small quantities of the carrier or

ligand drug are needed to produce the desired effect. Section 609 recognizes that the determination of the safety and effectiveness of such a radiopharmaceutical diagnostic or monitoring agent should include consideration of these unique characteristics and directs the FDA to develop regulations governing the approval of radiopharmaceuticals used for diagnostic and monitoring purposes. The provision states that the determination of safety and effectiveness should include consideration of the proposed use of the radiopharmaceutical in the practice of medicine, the pharmacological and toxicological activity of the radiopharmaceutical (including any carrier or ligand component), and the estimated absorbed radiation dose of the radiopharmaceutical. However, this provision is not intended to change the standards, or limit the data requirements, under section 505 of the Federal Food, Drug and Cosmetic Act or section 351 of the Public Health Service Act, by which the safety and effectiveness of such radiopharmaceuticals are determined.

In addition, section 610 acknowledges that the indications for which radiopharmaceuticals are used may, in appropriate cases, refer to manifestations of disease (such as biochemical, physiological, anatomic, or pathological processes) common to or present in 1 or more disease states. This refers to the fact that radiopharmaceutical diagnostic and monitoring agents may, under appropriate circumstances, be approved for use on the basis of their effectiveness in showing how a disease or process has developed, is developing, or is progressing.

This section is limited to radiopharmaceuticals used for diagnosis and monitoring and does not address radiopharmaceuticals used for therapeutic purposes. Thus, radiopharmaceutical is defined for purposes of this section only as (1) an article (A) that is intended for use in the diagnosis or monitoring of a disease or a manifestation of a disease in humans; and (B) which exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons; or (2) any nonradioactive reagent kit or nuclide generator which is intended to be used in the preparation of any such article.

Modernization of regulation of biological products

The provisions of section 351 of the Public Health Service Act that govern the FDA regulation of biological products were initially enacted by Congress in 1902 and were recodified in 1944. Responsibility for implementing these provisions was initially in other parts of the Public Health Service until it was transferred to the FDA in 1972. The basic concept of the statutory requirements has not been revised in more than 90 years.

When FDA assumed responsibility for regulating biological products in 1972, it made two important policy decisions. First, it retained a separate organizational structure and regulatory focus for biological products, rather than combining these products with new drugs. (Even when the two organizational structures were temporarily combined in the 1980's, a separate regulatory focus was maintained). Second, because biological products are also drugs, more recent regulatory concepts that were applied to new drugs, (e.g., compliance with drug GMP regulations) were incorporated

into the older system for biological products. In the past 25 years, the two regulatory systems have become similar, although each retains its separate identify.

The legislation takes this logical progression one step further. It substantially revises section 351 of the Public Health Service Act to make it much closer to the current approach for approval of new drugs. The most important revision repeals existing requirements for a facilities license. Since 1902, the law has been interpreted to require that the applicant for a new biological product ordinarily obtain both a product license and an establishment license. In contrast, the applicant for approval of anew drug is required to submit only a single application, which covers both the product and the manufacturing processes in the establishment. The legislation adopts the same approach for pioneer biological products as for new drugs. Thus, the current statutory requirement for licenses for biological products is clarified to require only one license—covering both the product and the facility in which the product is manufactured.

To ensure consistency in regulation of new drugs and biological products, the bill requires the FDA to take measures to minimize the differences in review and approval of products required to have biologics license applications under the revised section 351 of the Public Health Service Act and full new drug applications under section 505(b)(1) of the FFDCA. This requirement for harmonization does not apply in the case of generic products, however, since the authority for abbreviated new drug applications under section 505(j) is not applicable to biological products.

The FDA is required to establish, by regulations, the requirements that an applicant must meet in order to obtain approval of a biological product license application. The biological product must be demonstrated to be "safe, pure and potent". Potent is intended to mean "effectiveness" as FDA has historically interpreted the term. The applicant must also demonstrate compliance with GMP requirements. Preapproval inspection for compliance with GMP is included.

Among the most important biological products subject to FDA regulation are blood and products derived from blood. There are two basic categories of these products: (1) blood and blood components, and (2) products that are derived from blood and blood components. For currently licensed blood and its components, the FDA has established appropriate standards designed to assure safety, purity, and potency. The legislation is not intended to change FDA's ability to approve blood and its components that meet these standards. Blood and its components must also be obtained, held, processed, and utilized in accordance with GMP regulations. The safety determination for blood, blood components, and blood derivative products, as for other biological products, includes assessment of benefits and risks. There is always some degree of risk associated with blood and products made from blood.

Establishments that collect, process, and use blood and its components are uniquely located at the local community level. There are more than a thousand of these blood establishments, located throughout the country, in contrast with the usual situation with other pharmaceutical establishments. The committee intends that

regulatory requirements be streamlined and made efficient. For example, a single license application could cover all facilities under one management to utilize particular types of products or methods of processing when the application makes clear that all facilities and products meet applicable requirements and standards for their use. Requiring separate license applications for each separate facility and product can be wasteful of both industry and government resources and achieves no useful public health purpose.

It is important that, when a problem is found at a particular facility, the FDA has adequate power to revoke whatever licenses are applicable with respect to that specific location. If ten facilities are under one management and the FDA discovers that two fail to meet GMP requirements, or two are not properly using products or processes for which all of the facilities are licensed, FDA may suspend and revoke the applicable license with respect to those two facilities and their products.

Even before the FDA was delegated responsibility for the regulation of biological products, the FDA regulations governing investigational new drugs were used as the applicable requirements for the investigation of biological products as well. This practice is not changed under the legislation.

To simplify the statutory language, the legislation incorporates a definition of "biological product" to encompass all of the products that are presently included within the Public Health Service Act provisions governing this category of products. That defined term is then used throughout the new provision as well as in sections of the Food, Drug, and Cosmetic Act that apply to both biological products and non-biological new drugs.

Supplemental new drug applications

A new use of an approved drug can be added to the product label if the sponsor files a supplemental new drug application with FDA and FDA approves that application. Although the review times for these supplemental applications have improved over the past few years (in part due to the Prescription Drug User Fee Act of 1992), there are still many drug labels that do not reflect up-to-date information on new uses for approved products. Without adequate information about new uses on the drug label, there are risks of unsafe or inappropriate uses.

In an ideal world, common medical practice should be reflected on the FDA approved label for the product. In addition, the process for updating the label for an approved product should be sufficiently expeditious to justify the time and expense associated with the conduct of new clinical trials and submission of a supplemental approval application. In fact, however, there are many reasons why supplemental applications are not submitted, including:

Excessively high costs of a supplemental NDA (including the necessary clinical work) relative to the market for the new use, indication, or dosage;

Delays in the approval of supplements, which are currently running at one year from submission (as a median and a mean); and,

Patent or market exclusivity may expire.

In many cases products are prescribed for use, indications, or in doses that are not within the label approved by the FDA. In fact, many older, off-patent drugs are prescribed in this manner. According to the US General Accounting Office, one-third of all cancer drugs are used for uses other than that for which they were approved, 44 of 46 approved cancer drugs are used for at least one additional, non-approved use, and 56% of all cancer patients use at least one drug prescribed for a use other than that for which they were approved. This type of prescribing is also common with AIDS drugs—78% of all AIDS patients receive a drug in this manner. Overall, 80% of all prescription drugs are prescribed in a manner which differs in some respect from the approved labeling.

The legislation takes steps toward addressing this problem in several ways. First, it directs FDA to establish performance standards for the review of supplemental applications for approved products.

Second, FDA must issue final guidance documents that clarify the requirements for, and facilitate the submission of, data to support approval of such supplemental requirements. The guidance will clarify the circumstance in which published studies may be the basis for approval, specify data requirements that will avoid duplication of previously submitted data, and define supplemental applications that are eligible for priority review. FDA has already issued draft guidance documents that address most of these issues.

Third, the legislation requires FDA to designate an individual in each center (except the Center for Food Safety and Applied Nutrition) who will have responsibility for encouraging prompt review of supplemental applications and working with sponsors to facilitate the development and submission of data to support such supplemental applications.

Finally, FDA is directed to implement programs and policies to foster collaboration between FDA, the National Institutes of Health and others to identify published and unpublished studies to support supplemental applications and to encourage sponsors to make applications or conduct further research in support of an application based on such studies.

Health care economic information

The committee believes that the FDA should allow companies to share health economic information about approved "on label" uses for products under the same standard applied to over-the-counter drugs and other products. The agency currently requires these claims—which differ from efficacy claims—to be subjected to two clinical trials. The agency on several occasions conceded that this standard is inappropriate for such claims and agreed that it should be modified to a more appropriate standard.

Health economic information about approved "on label" uses is needed by managed care experts and other health care providers responsible for evaluating the benefits, other consequences, and costs of competing therapies. Health care providers also rely on companies to conduct studies in the providers' own or comparable representative populations to help the providers predict the specific benefits and costs of FDA-approved products for their particular organizations. Companies typically have the best and most com-

prehensive information about the cost, effectiveness, and safety of their products. The FDA should not unduly impede the flow of that information to experts who need it for patient and health plan decisions. Undue restrictions on the ability of companies to make competent and reliable claims on the basis of cost, effectiveness, or safety of approved uses of products interfere with the public health by encouraging the sale and use of needlessly expensive products.

This provision differentiates between clinical claims and economic claims. Clinical claims would continue to be governed by the evidence standard in the Act. Economic claims would be governed by the "competent and reliable scientific evidence standard used by the Federal Trade Commission, drawing from available evidence in the relevant economic fields of science. Economic claims could only be distributed to drug formulary committees, managed care entities, or similar entities with responsibility for drug selection decisions. Economic claims are defined as those that identify, measure, or compare the costs (direct, indirect, or intangible) and health care consequences of a drug to another drug or to another health care intervention for the same indication, or to no intervention, where the primary endpoint is an economic outcome of the research or analysis on which the statement is based.

Expediting approval and of fast-track drugs

The FDA currently has a number of mechanisms aimed at streamlining the development and approval process for new therapies for serious and life-threatening conditions. The committee believes that a formal statutory mechanism for identifying breakthrough drugs early in product development that provides sponsors of such drugs a reasonable opportunity for early interaction with the agency may help to further streamline the development and approval processes for such drugs.

This legislation is intended to clarify and coordinate some of FDA's mechanisms for new drugs and biological products that are intended for the treatment of serious and life threatening conditions and that demonstrate the potential to address unmet medical needs for such conditions. It defines and clarifies the processes pursuant to which sponsors of these drugs may interact with the FDA and includes provisions that will ensure that these processes are well known and well understood.

Pursuant to the legislation, drugs for serious and life threatening conditions that demonstrate the potential to address unmet medical needs will be eligible for a "fast track" designation. Sponsors may seek fast track designation concurrently with (or after) the submission of an application for the investigation of the drug. If the FDA determines that the drug should be designated as fast track, it will take appropriate action to expedite the development and review of the drug. For example, if preliminary evaluation of clinical efficacy data show evidence of effectiveness, FDA will evaluate for filing incomplete portions of the application and if the portion is filed, FDA may commence review of that portion. A sponsor will be eligible for this "rolling review," however, only if it has provided a schedule for submission of information necessary to make the application complete and any fee required under the Prescription Drug User Free Act.

The FDA may approve an application for approval of a fast track drug under section 505(b) or under section 351(a) of the Public Health Service Act upon a determination that the drug has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. This provision is not intended to change the standards under section 505 or section 351 of the Public Health Service Act, pursuant to which the safety and effectiveness of such drugs are determined. All fast track drugs must meet the evidentiary standards in section 505(d) or section 351(a) of the Public Health Service Act. Moreover, the Secretary may require the sponsor to conduct a post-approval study to validate the surrogate endpoint or otherwise confirm the clinical benefit of the drug. The Secretary also may require the sponsor to submit promotional materials during the pre-approval review period and following approval. The Secretary may withdraw approval of a fast track drug using expedited procedures if the sponsor fails to conduct required postmarketing studies, the post-approval study fails to verify clinical benefit, other evidence demonstrates that the drug is not safe or effective, or the sponsor disseminates promotional materials that are false or misleading. These expedite procedures include an opportunity for an informal hearing, as currently provided in FDA's accelerated approval regulation, rather than for a formal evidentiary hearing as provided in certain other circumstances.

In cases where there exists a surrogate endpoint which can be measured more rapidly than clinical endpoints and where a drug's effect on that surrogate endpoint is reasonably likely to predict clinical benefit, the acceptance of effects on surrogate endpoints as evidence of efficacy can lead to more rapid availability of safe and effective drugs for Americans with serious or life threatening illnesses. In order to reap that benefit, it is essential that potentially useful surrogate endpoints be identified and evaluated for their likelihood of predicting clinical benefit. To that end, it is the intent of Congress that the FDA participate with other public health agencies, patient groups, industry, academic, and medical groups and other interested parties in efforts to improve the utilization of surrogate endpoints. The committee is not directing the FDA to develop such surrogate endpoints, but rather is directing the agency to support the efforts of others to develop and validate surrogate endpoints.

This provision is not intended to modify any agreement reached under the Prescription Drug User Fee Act. The review periods agreed to under PDUFA will not begin to run until a complete application for a fast-track drug has been submitted to the agency.

To ensure that the processes and policies set forth in the fast-track provision are well known and well understood, this provision directs the Secretary to provide physicians, patient organizations, industry, and other appropriate persons a comprehensive description of the fast track provisions established under this legislation and within 1 year to issue guidance that describes the policies and procedures pertaining to fast-track drugs.

Finally, the committee recognizes that his opportunity for drugs to be approved on an urgent basis with what may be fewer data than are customary may require increasing reliance on post-approval studies to gather confirmatory or additional information.

The committee urges the industry to cooperate fully in the gathering of such post-approval studies in order to assure that drugs approved on a fast track are, indeed, safe and effective and to assure that patients and their providers are given information about the appropriate use of these drugs.

Manufacturing changes

The manufacturing processes and facilities used to produce a new drug or biological product undergo changes throughout the investigation of the product and after marketing approval is obtained from the FDA. Innovations are sought to reduce impurities, increase yield, reduce the complexity and time required for manufacture, eliminate equipment, automate procedures, increase stability, and otherwise to improve the drug and reduce its cost. The benefits of these innovations are passed on to the consumer in the form of improved products and lower prices.

In the past, the FDA has imposed very stringent limitations on the ability of the pharmaceutical and biotechnology industries to adopt new manufacturing procedures. For most manufacturing changes, FDA approval of the supplemental application is required. For only a few has the FDA permitted the change to be made immediately and simply reported to the FDA by a simultaneous supplement or in the annual report submitted to the FDA for the drug. For biological products, FDA has been even more stringent, requiring clinical trials to support new manufacturing processes in many situations. Supplemental applications for manufacturing changes have, moreover, traditionally been given a very low priority within the FDA. As a result, it can be years before a new manufacturing process can be used, even if it results in a substantial improvement in the drug.

The impact of past FDA policy in this area on the pharmaceutical and biotechnology industries has been substantial. First, many companies have established manufacturing facilities abroad, where they can use a modern process to supply a drug to the rest of the world long before they can use the same process to supply the United States. Second, some companies do not make important drug manufacturing improvements because of the cost and lengthy process required for approval. The development of new technology, the public health and pocketbook have all suffered.

To address these problems, the legislation considered by the committee included a new approach to manufacturing changes for new drugs and biological products. Current law governing manufacturing changes shall remain in effect until 24 months of the date of enactment of this legislation or the effective date of regulations promulgated by the FDA implementing the new policy, whichever is sooner. The policy focuses on the specifications of the drug or biological product found in the license application and sorts manufacturing changes into three categories. Major manufacturing changes, which are of a type determined by the FDA to have a substantial potential to adversely affect the identity, strength, quality, purity, and potency of a drug, as those characteristics relate to safety and efficacy, shall require prior approval of a supplemental application. The FDA will identify other types of manufacturing changes which can be made at will with only a requirement to note the change in

an annual report to the FDA. Other changes may be made, if FDA has not notified the company within 30 days after the submission of a supplement that a prior approval is required. FDA shall also designate changes for which distribution of the products may begin at the time the supplement is submitted. All supplements will continue to be approved or disapproved. If FDA later determines that the supplemental NDA is not immediately approvable, the agency will work with the applicant to resolve all issues and to assure the continued availability of the drug.

Food contact substances

This provisions adds to the FFDCA a premarket notification system that is intended to be the primary method by which FDA regulates food contact substances. The food additive petition process in its present form will continue to exist in the law, but will be invoked for food contact substances only in those cases where FDA determines that a petition is necessary to provide adequate assurance of safety or where a company and FDA agree that a petition may be submitted.

In creating the PMN system, this bill leaves in full force and effect the current food additive regulations covering food contact substances. It is not the intent of this legislation to require PMNs for materials that FDA already has received and found to be safe for their intended use.

This legislation also maintains the existing definition of "food additive" in Section 201(s) of the FFDCA (21 U.S.C. 321(s)). Therefore, a PMN will be required only for a food contact substance that is a "food additive" within the meaning of section 201(s). Similarly, a food contact substances that is a food additive but is not the subject of either a food additive regulation or an effective notification would be in violation of the food adulteration provision in section 401(a)(2)(C) of the FFDCA. Although the notification is effective for the purchaser of the substance manufactured by the notifier, the notification is not effective for other manufacturers of the same substance.

The legislation creates a premarket notification (PMN) system for clearance by the FDA of substances to be used in contact with food (i.e., food contact substances). Food contact substances include a variety of materials (e.g., plastics and paper), and their components, that are used to package, transport, hold, and manufacture food, which substances come in contact with food but are not intended to affect the food. Under the PMN system, any manufacturer or supplier may file with FDA a notification providing complete information supporting the safe use of a food contact substance. The notifying party may lawfully market and use the food contact substance 120 days after the date such a filing is received, unless FDA determines that the notifier has not provided information showing that the substance is safe, and informs the notifier of this determination and the basis for such determination.

The legislation provides an alternate system for the clearance of food contact substances that, in most cases, will replace for such substances the current food additive petition process established under the Food Additives Amendment of 1958. The legislation expressly provides that the petition process will remain available for

certain food contact substances. Section 617 will encourage and expedite the development and introduction of new food contact substances and new uses of existing substances without sacrificing the protection afforded consumers against unsafe substances in the food supply.

The need for this legislation arises from the fact that the Food Additives Amendment of 1958 requires FDA to regulate two different types of products in the same way, without due regard for their different public health and safety implications. These two categories of products are "direct food additives," which are intended to have a specific technical effect in the food and are intended to be ingested as part of the food supply, and "food contact substances" (often described as "indirect food additives" under the current regulatory system), which are intended to contact food but are not intended to have a technical effect in the food and whose ingestion is incidental to their use.

Under the Food Additives Amendment of 1958, both categories of substances are subject to the same regulatory procedures and requirements in that both must go through the full food additive petition process. Furthermore, (with the exception of substances regulated under 21 CFR § 170.39), lawful use of either a direct food additive or a food contact substance requires, following FDA safety review, publication of a regulation in the Federal Register specifying the conditions under which the substance can be safely used.

FDA regulation of these two different classes of products in the same way results in a significant expenditure of resources by the agency and by the industry on the premarket clearance of food contact substances that in many cases is out of proportion to any resulting increase in public health protection. Petitions for regulation of food contact substances outnumber those for direct additives by a substantial margin. At present, FDA does not have the resources to complete the review of all food additive petitions for food contact substances within the current statutory time frame of 180 days and also carry out its other important public health responsibilities, including review of direct additives.

The committee is aware that reports indicate that the many companies in the United States which now market globally are experiencing even more severe delays in securing product clearances in those parts of the world that are adopted regulatory approaches for food contact materials similar to that used here since 1958. Adoption of the PMN concept may provide a useful model for changes in the rest of the world and could, thereby, advance the goal of international harmonization of regulatory systems.

Most food contact substances pose relatively little potential risk to consumers because their use results in only very low potential exposure to the substances in the diet. Indeed, the Agency in recent years has implemented initiatives to expedite and review of low-risk food contact substances. These initiatives include implementation of a Threshold of Regulation (TOR) rule, under which FDA has exempted from the need for a food additive regulation food additives that are used at a level that results in a dietary concentration below the threshold set in the rule. The TOR approach to regulating food additives is a thoroughly developed public policy, which has been widely and publicly debated.

The premarket notification program builds upon FDA's almost 40 years of experience in reviewing and regulating food contact substances, and upon its more recent experience with the TOR approach to the review of low-risk additives. Such a program will continue to ensure the safe use of these additives, without requiring agency premarket review of food additive petitions and publication of orders in the Federal Register. Because of considerations such as level of consumption or potential toxicity, the committee recognizes that some uses of food contact substances may require premarket review and approval under § 409 in order to ensure their safe use. The legislation is thus drafted to permit the agency to exclude those uses of food contact substances from eligibility for premarket notification, based on its experience with the safety review of these food additives. A premarket notification system for food contact substances would improve allocation of scarce agency resources by allowing the agency to reduce the resources spent on reviewing low-risk food additives, including most food contact substances. This more efficient use of resources will allow the Agency to focus on premaket review of those additives with the greatest potential for risk to consumers.

A PMN is intended to be specific to the manufacturer or supplier that files it and the particular product that is the subject of the notification. This approach differs from food additive regulations, which are generic regulations that permit anyone, not just the petitioner, to manufacture the food additive (subject to any patent restrictions). For the regulated industry, there will still be costs associated with preparing and filing a PMN that provides much of the same information currently required for a food additive petition. However, because of the shorter turnaround time, increased predictability, and proprietary nature of the PMN, these costs will be recouped much more quickly.

FDA also will benefit from the PMN system. The demands on the agency's resources to address food contact substances will be brought into line with the low potential risk associated with most of these products. As a result, the PMN system for food contact substances should free resources for dedication to more pressing issues.

FDA also is likely to receive more information on the use of all food contact substances in the American food supply since more manufacturers and suppliers are likely to submit PMN's than currently submit food additive petitions. In addition, the increased predictability will increase the incentive for companies to make FDA aware of new uses of food contact substances. As a result, the agency should have an improved data base to assess total exposure to food contact materials. These additional data will ultimately benefit the public health by providing FDA with more information on the identity and levels of food contact substances in use. FDA will then be able to more effectively monitor these substances and respond to any public health problems that may arise.

Health claims of food products

This legislation makes amendments to section 403(r) of the Federal Food, Drug, and Cosmetic Act to authorize truthful, nonmisleading health claims that are based on the published authoritative

statements of scientific bodies of the U.S. Government with official responsibility for public health protection or research directly relating to human nutrition.

It has been the concern of the Congress from the start of the nutrition labeling reform process begun nearly a decade ago that health claims be authorized when they are supported by appropriate scientific evidence and are stated in a truthful, nonmisleading manner. Such claims serve the public health by helping to disseminate important health information to the public promptly, and at the point of purchase where they can help shape healthful consumer food choices.

Under existing section 403(r)(3), health claims can be made for food only after FDA issues a regulation authorizing the specific claim. This same preclearance requirement applies to all health claims—from the novel claim, to the claim that would be supported by the authoritative statement of an official public health agency of the Federal Government. This procedure is inefficient and fails adequately to benefit from the deliberative processes in which authoritative scientific bodies engage in issuing statements on matters of public health. Important Federal public health organizations, as part of their official responsibilities, routinely review the scientific evidence pertinent to diet and disease relationships, and publish statements developed through such reviews. The Surgeon General and National Academy of Sciences have published authoritative reports on such relationships. The National Cancer Institute has issued pamphlets recommending food choices to reduce the risk of cancer. The National Heart, Lung, and Blood Institute has issued a range of authoritative publications aimed at reducing the risk of hypertension and heart disease in the United States population.

The failure of the current system to give adequate weight to the statements of such authoritative bodies, coupled with the prohibitive economic burden that permits only the largest food companies and trade organizations to file a health claim petition to gain approval of a new health claim, has deprived the public of the full disease prevention benefits health claims were intended to provide.

This legislation maintains the rigorous scientific standard health claims must meet under existing law but streamlines the procedure for making health claims when the scientific basis for a claim has been developed by an authoritative scientific body outside FDA. This procedure targets regulatory resources more effectively, and promises to benefit public health substantially more than the current system.

The history of the folic acid and neural tube defects health claim dramatizes the critical need for this legislation. In 1992, the Centers for Disease Control and Prevention (CDC) issued the following recommendation to women of childbearing age, aimed at reducing the risk of pregnancies affected by neural tube birth defects:

> All women of childbearing age in the United States who are capable of becoming pregnant should consume 0.4 mg of folic acid per day for the purpose of reducing their risk of having a pregnancy affected with spina bifida or [other neural tube defects].

Centers for Disease Control, 41 *Morbidity and Mortality Weekly Report* (September 11, 1992). The CDC estimated that this recommendation could reduce the number of cases of spina bifida and other neural tube defects in the United States by 50 percent.

Despite the significant scientific agreement among qualified experts concerning the evidence supporting the recommendation, manufacturers of foods containing folic acid were prohibited from making claims about the benefit of folic acid in reducing the risk of neural tube defects until FDA approved the claim through a notice and comment rulemaking procedure.

Without appropriately accounting for the CDC recommendation, FDA promulgated a rule in January 1993, prohibiting claims concerning the relationship. In the wake of controversy concerning FDA's action, and despite the absence of any change in the scientific evidence, the Agency reversed course, proposing to authorize such claims in October, 1993. Final regulations authorizing the claim were promulgated in March 1996. Undoubtedly, many children suffered from preventable neural tube defects as a result of FDA's delay in authorizing health claims based on the 1992 CDC recommendation.

The amendments this legislation makes to section 403(r)(3) of the Federal Food Drug and Cosmetic Act would prevent a recurrence of the kind of problem presented by the folic acid/neural tube defect claim. While the legislation makes no change to the existing standards governing the health claim approval process, it establishes an alternative procedure by which health claims supported by an authoritative statement of an appropriate scientific body of the U.S. Government are authorized. Such claims could be made after premarket notification to FDA, without the delay that accompanies the rulemaking process. The legislation would require manufacturers intending to make such a health claim to submit a premarket notice to FDA concisely describing the claim and the authoritative statement relied upon. The notice would be submitted at least 120 days before the first introduction of a food bearing the claim into interstate commerce.

Although the legislation would eliminate the requirement for FDA approval of such claims, it would continue to require foods to conform to the "disqualifying nutrient levels" established by FDA under section 403(r)(3)(A)(ii) and require all health claims to be presented in a truthful, nonmisleading manner in conformance with sections 403(a) and 201(n) of the Federal Food Drug and Cosmetic Act. For example, a food bearing a truthful health claim based on an authoritative statement would need to make a material dietary contribution of the substance to which the claim refers to meet the requirements of sections 403(a) and 201(n). The legislation specifically mandates that a health claim accurately represent the authoritative statement on which it is based, and be presented in a manner enabling the public to comprehend the significance of the claim in the context of a total diet.

The agency retains full authority to take enforcement action against a health claim that mischaracterizes the authoritative statement upon which it is based, or that is otherwise misleading. The 120 day premarket notice requirement would enable FDA to identify misleading claims and take action to prevent their use be-

fore products bearing such claims are introduced to the market. In response to notifications filed by dietary supplement manufacturers concerning claims made under section 403(r)(6) of the Act, a provision adopted as part of the Dietary Supplement Health and Education Act of 1994, FDA issues "courtesy letters" promptly alerting manufacturers when claims submitted in their notification present a risk of enforcement action. Such an approach is an efficient and effective means of deterring manufacturers from making violative claims.

Under this legislation, the agency retains the full range of enforcement powers it has possessed historically to remedy misleading claims, including the powers of product seizure, injunction, and criminal penalties. In addition, new section 403(r)(3)(D) assures that FDA retains full authority to regulate health claims based on the statements of authoritative bodies through rulemaking. Once FDA regulations governing health claims concerning a particular diet/disease relationship (e.g., calcium and osteoporosis) have become effective, no claim concerning that diet/disease relationship based on the statement of an authoritative scientific body could be made unless it is consistent with the FDA regulation. The legislation specifically provides that FDA may prohibit or modify such health claims through rulemaking. In any such proceeding, the standards and criteria for health claims prescribed in section 403(r)(3) and implementing regulations, including the significance scientific agreement standard, would be fully applicable.

Pediatric studies of drugs

When it comes to pharmaceuticals, our Nation's children are "therapeutic orphans." Currently, less than 20 percent of the prescription medications on the United States market are approved for use in the pediatric population and labeled for pediatric use. Pediatricians using drugs developed with adults in mind but which may also be effective or be the only option for treating the same illnesses and diseases in children must estimate dosages from dosages found to be safe and effective in adults. Such estimates are uncertain because children, and particularly those under 2 years of age, often metabolize drugs differently than do adults. Further, some drugs have different side effects and/or toxicities in children than in adults even when appropriate doses are used.

For these reasons, pediatricians have long had an active interest in promoting clinical studies of drugs in pediatric populations so that the drugs may be labeled for pediatric use. However, there is little incentive for drug sponsors to perform studies for medications which they intend to market primarily for adults and whose use in children is expected to generate little additional revenue. Pediatric studies pose ethical and moral issues relating to using new unapproved drugs in young patients. Second, there are substantial product liability and medical malpractice issues. Third, pediatric patients are more difficult to attract into studies. Fourth, for some drugs, pediatric use represents more difficult issues of drug administration and patient compliance than adult use.

The FDA has sought to address this problem by using its authority to approve labeling based upon the known pharmacokinetics of the drug, as opposed to requiring pediatric clinical trials for effi-

cacy. The FDA has also issued regulations that embody this policy in an attempt to encourage pediatric labeling. These are clearly steps in the right direction, and the committee commends the FDA's initiatives in this area.

The legislation takes a modest further step toward a better resolution of this problem by providing an additional 6 months of market exclusivity when a drug manufacturer, at the request of the FDA, conducts pediatric studies to support pediatric labeling for a drug, either before the new drug approval application is submitted or later.

Positron emission tomography

The committee intends in section 619 to provide a new framework for the regulation of radiotracers used in positron emission tomography (PET) scans based on standards set by the United States Pharmacopoeia (USP) and enforced by the FDA and state boards of pharmacy and medicine.

The committee intends to require that PET radiotracers meet the standards set by the USP for safety, efficacy and compounding, and that the FDA or state agencies will enforce the standards set by the USP. The Committee does not intend that the FDA set its own standards for compounding of PET drugs. Makers and users of PET radiotracers will continue to be subject to the requirements of the various state boards of medicine and pharmacy which they are currently required to meet.

USP standards are recognized in the FFDCA in the adulteration and misbranding sections of the Act (Secs. 501(b) and 502 respectively). USP establishes standards for all marketed drugs in the U.S. It first provided standards for PET pharmaceuticals in 1988. During these years, USP standards have served to standardize and help assure the quality of these items and protect the public health. USP establishes standards for drugs through a rigorous peer reviewed process, and the FDA provides input and comment to USP as part of this process.

Section 619(a) amends the FFDCA to add a definition of a "compounded positron emission tomography drug" to mean a PET drug (and associated software and hardware) which has been compounded in accordance with State law by or on the order of a practitioner licensed in that State or in a Federal facility in accordance with the law of the State in which it is located.

Section 619(b) amends the FFDCA to provide that a compounded PET drug is adulterated, and thus subject to regulatory and/or legal action by FDA, if it is compounded, processed, packed, or held other than in accordance with the PET compounding standards and the official monographs of the USP.

Section 619(c) amends the FFDCA to provide that neither a New Drug Application (NDA) nor an Abbreviated New Drug Application (ANDA) is required by a licensed practitioner to produce a compounded PET drug produced in accordance with USP standards.

Section 619(d) requires the revocation of certain Federal Register notices which announced a rule inconsistent with this legislation.

PET is an imaging technique that produces a computerized image (scan) using small quantities of a radioactive tracer to meas-

ure biochemical activity in the body. It has been demonstrated to be an extremely effective method of separating benign from malignant lesions, staging the degree of metastasis, determining therapeutic effectiveness and identifying early recurrence of disease in several types of cancer, including lung, breast, colorectal, head and neck. In addition, PET has a high degree of accuracy in identifying early signs of coronary artery disease and in assessing whether cardiac tissue is alive following a heart attack. In more than one million uses of PET tracers in Europe and one million in the United States, the Committee is unaware of any reported instance of an adverse reaction to PET radiotracers. PET radiopharmaceuticals have been used in patients in the United States for over 30 years. Recent research and advances in imaging technology have enhanced the clinical importance of PET.

PET radiotracers are unique among radiopharmaceuticals because of their short half-lives, ranging from 30 seconds to 110 minutes. Therefore, most PET radiotracers are made using a cyclotron which is at or near the PET site, and most are made up on an individual dose basis upon the prescription of a licensed physician. At present, there are 70 PET centers in the United States, almost all of which are part of academic medical centers. PET technology and its applications were developed in large part with almost $2 billion in federal research funds. Yet, while PET is widely used in Europe, its benefits have not been widely available to American patients, mainly because of lack of reimbursement and inappropriate and costly regulations promulgated by FDA.

Under current FDA regulations, PET centers which compound PET radiopharmaceuticals on an individual dose basis would be required to meet FDA's CGMP and to file NDA's and ANDA's for each type of PET tracer and for each indication for which the tracer might be used. This is the same type of regulation which the FDA applies to large pharmaceutical manufacturers.

Academic medical centers are facing unprecedented cost pressures. Without regulatory relief and expanded reimbursement, particularly from the Medicare program, many PET centers are likely to close, and the benefits of PET will be unavailable to the taxpayers who funded their development. For example, the University of California at Los Angeles estimated that FDA's new PET regulations would cost the University at least $300,000 for a single application for a single use of a PET radiotracer.

The committee intends that adoption of this section will establish a regulatory framework for PET drugs that will enable PET centers to continue to make this valuable technology available to patients at reasonable cost and assure that the public health will be protected.

TITLE VII—FEES RELATING TO DRUGS

The legislation reauthorizes the Prescription Drug User Fee Act of 1992 (PDUFA I) to allow the continued collection of user fees from prescription drug manufacturers for five additional years. PDUFA I represented a consensus among the FDA, the prescription drug industry, and Congress that the industry would pay user fees to augment the resources of the FDA devoted to the review of

human drug applications. PDUFA I has succeeded in substantially reducing review times for human drug applications.

The PDUFA I legislation was accompanied by side letters signed by the Commissioner of Food and Drugs and the Chairs and Ranking Minority Members of the House Energy and Commerce Committee and the Senate Labor and Human Resources Committee. The side letters committed FDA to achieving certain performance measures including:

Review and act on priority new drug and biologic applications within 6 months:

Review and act on standard new drug and biologic applications with 12 months;

Review and act on priority supplements and amendments within 6 months;

Review and act on standard supplements and amendments that do not require clinical data within 6 months;

Review and act on standard supplements and amendments with clinical data within 12 months; and

Review and act on resubmitted applications within 6 months.

Title VII of S. 830 (PDUFA II) would build on PDUFA I by including new commitments from FDA to implement more ambitious and comprehensive improvements in its regulatory process. PDUFA I focused on reducing the length of time taken by FDA in reviewing an application. The committee commends FDA for successfully meeting and at times exceeding the performance goals established in PDUFA I. However, while review times for submitted applications have improved, the period of time taken to get a drug through the drug development phase has increased from 2 years to seven years. Appropriately, PDUFA II will focus on shortening overall development time and streamlining interaction with FDA required of a drug innovator during the highly regulated drug development phase and establish new performance measures and procedures for FDA designed to reduce the amount of time needed to take a drug from clinical testing phase to the point where an application may be submitted for review.

The legislation provides that the FDA's fiscal year 1997 appropriations will become the new PDUFA baseline appropriation, adjusted for inflation after fiscal year 1998, over the next five years. The bill assumes that for Fiscal year 1998, FDA will receive at least the Fiscal year 1997 level of appropriated funds for salaries and expenses. It specifies exactly what the application and supplemental fees will be per product for the next five years, subject to adjustment for inflation. In addition, it defines small businesses as those with fewer than 500 employees, and allows a waiver for such businesses fee payments on their first human drug applications. FDA would continue to be required to send Congress annually a financial report on how it spent PDUFA fees and report on whether and how FDA met the new performance goals which focus on expediting the drug development process and the review of human drug applications.

The differences between PDUFA I and PDUFA II can be divided into two categories. The first category of changes pertains to financial provisions and performance goals. Among other things, these changes include the increase in fees from PDUFA I to accommodate

enhanced performance by FDA and the adjustment of total fees each year to reflect a changing FDA workload. As with PDUFA I, revised performance goals will be set forth in letters from the Secretary of the Department of Health and Human Services official to the Chairman and Ranking Minority Members of the House Commerce Committee and Senate Committee on Labor and Human Resources. This letter is incorporated by reference in the Findings section of Title VII of the bill. The committee intends that the provisions be fully binding on the agency and should be considered as minimum not maximum commitments.

The second category of changes includes technical changes and other improvements which primarily relate to fee collection and exemptions from fees, including language providing the Secretary flexibility to take into account special circumstances associated with user fee waiver applications. These special circumstances may include the ability to stimulate innovation in biomedical research by providing special waivers or discounts to applicants participating in innovative research development projects located in Federal empowerment and enterprise zones. A detailed review of the performance goals and other measures covered by PDUFA II, referenced in Section 702 of the bill, are reflected in the exchange of letters that follow below.

These performance measures, agreed to by FDA officials and the boards of the Biotechnology Industry Organization and the Pharmaceutical Research and Manufacturers of America, are contingent upon the level of appropriated funds for the FDA set forth in the legislation. The committee observes that PDUFA I was successful in large part because the underlying assumption regarding steadily increasing appropriations levels available to FDA was in fact borne out. The committee cautions that this key assumption can not be taken for granted over the next five years in light of the overriding imperative to reduce the Federal budget deficit and the complicating factors contributed by the President's proposed budget cut for the FDA in fiscal year 1998.

Finally, the committee notes that the Food, Drug, and Cosmetic Act gives the Secretary of HHS discretion to grant a waiver from, or a reduction of 1 or more user fees where the Secretary finds "the assessment of the fee would present a significant barrier to innovation because of limited resources available to such person or other circumstances." This language is intended to provide the Secretary flexibility to take into account special circumstances associated with user fee waiver applications including the ability to stimulate innovation in biomedical research by providing special waivers or discounts to applicants participating in innovative research development projects in federal empowerment and enterprise zones.

PROPOSED PDUFA II PERFORMANCE GOALS AND PROCEDURES

The proposed performance goals and procedures of the FDA Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), contingent upon resolution of Agency and program budget issues, are summarized as follows:

A. FIVE-YEAR REVIEW PERFORMANCE GOALS

Fiscal year 1998

1. Review and act on 90 percent of standard original New Drug Application (NDA's) and Product License Applications (PLA's)/Biologic License Applications (BLA's) filed during fiscal year 1998 within 12 months of receipt.
2. Review and act on 90 percent of priority original NDA and PLA/BLA submissions filed during fiscal year 1998 within 6 months of receipt.
3. Review and act on 90 percent of standard efficacy supplements filed during fiscal year 1998 within 12 months of receipt.
4. Review and act on 90 percent of priority efficacy supplements filed during fiscal year 1998 within 6 months of receipt.
5. Review and act on 90 percent of manufacturing supplements filed during fiscal year 1998 within 6 months of receipt.
6. Review and act on 90 percent of all resubmitted original applications filed during fiscal year 1998 within 6 months of receipt, and review and act on 30 percent of class 1 resubmitted original applications within 2 months of receipt.

Fiscal year 1999

1. Review and act on 90 percent of standard original NDA and PLA/BLA submissions filed during fiscal year 1999 within 12 months of receipt and review and act on 30 percent within 10 months of receipt.
2. Review and act on 90 percent of priority original NDA and PLA/BLA submissions filed during fiscal year 1999 within 6 months of receipt.
3. Review and act on 90 percent of standard efficacy supplements filed during fiscal year 1999 within 12 months of receipt and review and act on 30 percent within 10 months of receipt.
4. Review and act on 90 percent of priority efficacy supplements filed during fiscal year 1999 within 6 months of receipt.
5. Review and act on 90 percent of manufacturing supplements filed during fiscal year 1999 within 6 months of receipt and review and act on 30 percent of manufacturing supplements requiring prior approval within 4 months of receipt.
6. Review and act on 90 percent of class 1 resubmitted original applications filed during fiscal year 1999 within 4 months of receipt and review and act on 50 percent within 2 months of receipt.
7. Review and act on 90 percent of class 2 resubmitted original applications filed during fiscal year 1999 within 6 months of receipt.

Fiscal year 2000

1. Review and act on 90 percent of standard original NDA and PLA/BLA submissions filed during fiscal year 2000 within 12 months of receipt and review and act on 50 percent within 10 months of receipt.
2. Review and act on 90 percent of priority original NDA and PLA/BLA submissions filed during fiscal year 2000 within 6 months of receipt.

3. Review and act on 90 percent of standard efficacy supplements filed during fiscal year 2000 within 12 months of receipt and review and act on 50 percent within 10 months of receipt.

4. Review and act on 90 percent of priority efficacy supplements filed during fiscal year 2000 within 6 months of receipt.

5. Review and act on 90 percent of manufacturing supplements filed during fiscal year 2000 within 6 months of receipt and review and act on 50 percent of manufacturing supplements requiring prior approval within 4 months of receipt.

6. Review and act on 90 percent of class 1 resubmitted original applications filed during fiscal year 2000 within 4 months and review and act on 50 percent within 2 months of receipt.

7. Review and act on 90 percent of class 2 resubmitted original applications filed during fiscal year 2000 within 6 months of receipt.

Fiscal year 2001

1. Review and act on 90 percent of standard original NDA and PLA/BLA submissions filed during fiscal year 2001 within 12 months of receipt and review and act on 70 percent within 10 months of receipt.

2. Review and act on 90 percent of priority original NDA and PLA/BLA submissions filed during fiscal year 2001 within 6 months of receipt.

3. Review and act on 90 percent of standard efficacy supplements filed during fiscal year 2001 within 12 months of receipt and review and act on 50 percent within 10 months of receipt.

4. Review and act on 90 percent of priority efficacy supplements filed during fiscal year 2001 within 6 months of receipt.

5. Review and act on 90 percent of manufacturing supplements filed during fiscal year 2001 within 6 months of receipt and review and act on 70 percent of manufacturing supplements requiring prior approval within 4 months of receipt.

6. Review and act on 90 percent of class 1 resubmitted original applications filed during fiscal year 2001 within 4 months and review and act on 70 percent within 2 months of receipt.

7. Review and act on 90 percent of class 2 resubmitted original applications within 6 months of receipt.

Fiscal year 2002

1. Review and act on 90 percent of standard original NDA and PLA/BLA submissions filed during fiscal year 2001 within 12 months of receipt.

2. Review and act on 90 percent of priority original NDA and PLA/BLA submissions filed during fiscal year 2001 within 6 months of receipt.

3. Review and act on 90 percent of standard efficacy supplements filed during fiscal year 2001 within 10 months of receipt.

4. Review and act on 90 percent of priority efficacy supplements filed during fiscal year 2001 within 6 months of receipt.

5. Review and act on 90 percent of manufacturing supplements filed during fiscal year 2001 within 6 months of receipt and review and act on 90 percent of manufacturing supplements requiring prior approval within 4 months of receipt.

6. Review and act on 90 percent of class 1 resubmitted original applications within 6 months of receipt.

7. Review and act on 90 percent of class 2 resubmitted original applications within 6 months of receipt.

These review goals are summarized in the following tables:

Original NDA's/BLA's/PLA's and Efficacy Supplements:

Submission cohort	Standard	Priority
Fiscal year 1998	90 percent in 12 mo	90 percent in 6 mo.
Fiscal year 1999	30 percent in 10 mo 90 percent in 12 mo	90 percent in 6 mo.
Fiscal year 2000	50 percent in 10 mo 90 percent in 12 mo	90 percent in 6 mo.
Fiscal year 2001	70 percent in 10 mo 90 percent in 12 mo	90 percent in 6 mo.
Fiscal year 2002	90 percent in 10 mo	90 percent in 6 mo.

Manufacturing supplements:

Submission cohort	Manufacturing supplements that do not require prior approval (''changes being effected'' or ''30-day supplements''	Manufacturing supplements that do require prior approval
Fiscal year 1998	90 percent in 6 mo	90 percent in 6 mo.
Fiscal year 1999	90 percent in 6 mo	30 percent in 4 mo. 90 percent in 6 mo.
Fiscal year 2000	90 percent in 6 mo	50 percent in 4 mo. 90 percent in 6 mo.
Fiscal year 2001	90 percent in 6 mo	70 percent in 4 mo. 90 percent in 6 mo.
Fiscal year 2002	90 percent in 6 mo	90 percent in 4 mo.

Resubmission of original NDA's/BLA's/PLA's:

Submission cohort	Class 1	Class 2
Fiscal year 1998	90 percent in 6 mo 30 percent in 2 mo	90 percent in 6 mo.
Fiscal year 1999	90 percent in 4 mo 50 percent in 2 mo	90 percent in 6 mo.
Fiscal year 2000	90 percent in 4 mo 70 percent in 2 mo	90 percent in 6 mo.
Fiscal year 2001	90 percent in 2 mo	90 percent in 6 mo.
Fiscal year 2002	90 percent in 2 mo	90 percent in 6 mo.

B. NEW MOLECULAR ENTITY (NME) PERFORMANCE GOALS

The performance goals for standard and priority original NME's in each submission cohort will be the same as for all of the original NDA's (including NME's) in each submission cohort but shall be reported separately.

For biological products, for purposes of this performance goal, all original BLAs/PLAs will be considered to be NMEs.

C. MEETING MANAGEMENT GOALS

1. Responses to meeting requests

a. Procedure: Within 14 calendar days of the agency's receipt of a request from industry for a formal meeting (i.e., a scheduled face-to-face, teleconference, or videoconference) CBER and CDER should notify the requester in writing (letter or fax) of the date, time, and place for the meeting, as well as expected Center participants.

b. Performance Goal: FDA will provide this notification within 14 days for 70 percent of requests (based on request receipt cohort year) starting in FY99; 80 percent in FY00; and 90 percent in subsequent fiscal years.

2. Scheduling meetings

a. Procedure: The meeting date should reflect the next available date on which all applicable Center personnel are available to attend, consistent with the component's other business; however, the meeting should be scheduled consistent with the type of meeting requested. If the requested date for any of these types of meetings is greater than 30, 60, or 75 calendar days (as appropriate) from the date the request is received by the agency, the meeting date should be within 14 calendar days of the date requested.

Type A meetings should occur within 30 calendar days of the agency receipt of the meeting request.

Type B meetings should occur within 60 calendar days of the agency receipt of the meeting request.

Type C meetings should occur within 75 calendar days of the agency receipt of the meeting request.

b. Performance goal: 70 percent of meetings are held within the timeframe (based on cohort year of request) starting in FY99; 80 percent in FY00; and 90 percent in subsequent fiscal years.

3. Meeting minutes

a. Procedure: The agency will prepare minutes which will be available to the sponsor 30 calendar days after the meeting. The minutes will clearly outline the important agreements, disagreements, issues for further discussions, and action items from the meeting in bulleted form and need not be in great detail.

b. Performance goal: 70 percent of minutes are issued within 30 calendar days of date of meeting (based on cohort year of meeting) starting in FY99; 80 percent in FY00; and 90 percent in subsequent fiscal years.

4. Conditions

For a meeting to qualify for these performance goals:

a. A written request (letter or fax) should be submitted to the review division; and

b. The letter should provide:

i. A brief statement of the purpose of the meeting;

ii. A listing of the specific objectives/outcomes the requester expects from the meeting;

iii. A proposed agenda, including estimated times needed for each agenda item;

iv. A listing of planned external attendees;

v. A listing of requested participants/disciplines representative(s) from the Center;

vi. The approximate time that supporting documentation (i.e., the "backgrounder") for the meeting will be sent to the Center (i.e., "x" weeks prior to the meeting, but should be received by the Center at least 2 weeks in advance of the scheduled meeting for Type or C meetings and at least

1 month in advance of the scheduled meeting for Type B meetings; and

c. The agency concurs that the meeting will serve a useful purpose (i.e., it is not premature or clearly unnecessary). However, requests for a "Type B" meeting will be honored except in the most unusual circumstances.

D. CLINICAL HOLDS

1. Procedure: The Center should respond to a sponsor's complete response to a clinical hold within 30 days of the agency's receipt of the submission of such sponsor response.

2. Performance goal: 75 percent of such responses are provided within 30 calendar days of the Agency's receipt of the sponsor's response starting in FY98 (cohort of date of receipt) and 90 percent in subsequent fiscal years.

E. MAJOR DISPUTE RESOLUTION

1. Procedure: For procedural or scientific matters involving the review of human drug products (as defined in PDUFA) that cannot be resolved at the divisional level (including a request for reconsideration by the Division after reviewing any materials that are planned to be forwarded with an appeal to the next level), the response to appeals of decisions will occur within 30 calendar days of the Center's receipt of the written appeal.

2. Performance goal: 70 percent of such answers are provided within 30 calendar days of the Center's receipt of the written appeal starting in FY99; 80 percent in FY00; and 90 percent in subsequent fiscal years.

3. Conditions.

a. Sponsors should first try to resolve the procedural or scientific issue at the Division level. If it cannot be resolved at that level, it should be appealed to the Office Director level (with a copy to the Division Director) and then, if necessary, to the Deputy Center Director or Center Director (with a copy to the Office Director).

b. Responses should be either verbal (followed by a written confirmation within 14 calendar days of the verbal notification) or written and should ordinarily be to either deny or grant the appeal.

c. If the decision is to deny the appeal, the response should include reasons for the denial and any actions the sponsor might take in order to persuade the agency to reveres its decision.

d. In some cases, further data or further input from others might be needed to reach a decision on the appeal. In these cases, the "response" should be the plan for obtaining that information (e.g., requesting further information from the sponsor, scheduling a meeting with the sponsor, scheduling the issue for discussion at the next scheduled available advisory committee).

e. In these cases, once the required information is received by the agency (including any advice from an advisory committee), the person to whom the appeal was made, again has 30 calendar days from the receipt of the required information in which to either deny or grant the appeal.

f. Again, if the decision is to deny the appeal, the response should include the reasons for the denial and any actions the spon-

sor might take in order to persuade the agency to reverse its decision.

g. N.B.: If the agency decides to present the issue to an advisory committee and there are not 30 days before the next scheduled advisory committee, the issue will be presented at the following scheduled committee meeting in order to allow conformance with advisory committee administrative procedures.

F. SPECIAL PROTOCOL QUESTION ASSESSMENT AND AGREEMENT

1. Procedure: Upon specific request by a sponsor (including specific questions that the sponsor desires to be answered), the agency will evaluate certain protocols and issues to assess whether the design is adequate to meet scientific and regulatory requirements identified by the sponsor.

a. The sponsor should submit a limited number of specific questions about the protocol design and scientific and regulatory requirements for which the sponsor seeks agreement (e.g., is the dose range in the carcinogenicity study adequate, considering the intended clinical dosage; are the clinical endpoints adequate to support a specific such an.

b. Within 45 days of agency receipt of the protocol and specific questions, the agency will provide a written response to the sponsor that includes a succinct assessment of the protocol and answers to the questions posed by the sponsor. If the agency does not agree that the protocol design, execution plans, and data analyses are adequate to achieve the goals of the sponsor, the reasons for the disagreement will be explained in the response.

c. Protocols that qualify for this program include: carcinogenicity protocols, stability protocols, and Phase 3 protocols for clinical trials that will form the primary basis of an efficacy claim. (For such Phase 3 protocols to qualify for this comprehensive protocol assessment, the sponsor must have had an end of Phase 2/pre-Phase 3 meeting with the review division so that the division is aware of the developmental context in which the protocol is being reviewed and the questions being answered.)

d. N.B.: For products that will be using Subpart E or Subpart H development schemes, the Phase 3 protocols mentioned in this paragraph should be construed to mean those protocols for trials that will form the primary basis of an efficacy claim no matter what phase of drug development in which they happen to be conducted.

e. If a protocol is reviewed under the process outlined above and agreement with the agency is reached on design, execution, and analyses and if the results of the trial conducted under the protocol substantiate the hypothesis of the protocol, the agency agrees that the data from the protocol can be used as part of the primary basis for approval of the product. The fundamental agreement here is that having agreed to the design, execution, and analyses proposed in protocols reviewed under this process, the agency will not later alter its perspective on the issues of design, execution, or analyses unless public health concerns unrecognized at the time of protocol assessment under this process are evident.

2. Performance goal: 60 percent of special protocols assessments and agreement requests completed and returned to sponsor within

timeframes (based on cohort year of request) starting in FY 99; 70 percent in FY00; 80 percent in Fiscal year 01; and 90 percent in FY02.

G. ELECTRONIC APPLICATIONS AND SUBMISSIONS

The agency shall develop and update its information management infrastructure to allow, by fiscal year 2002, the paperless receipt and processing of INDs and human drug applications, as defined in PDUFA, and related submissions.

H. ADDITIONAL PROCEDURES

1. Simplification of Action Letters.

To simplify regulatory procedures, the CBER and the CDER intend to amend their regulations and processes to provide for the issuance of either an "approval" (AP) or a "complete response" (CR) action letter at the completion of a review cycle for a marketing application.

2. Timing of Sponsor Notification of Deficiencies in Applications.

To help expedite the development of drug and biologic products, CBER and CDER intend to submit deficiencies to sponsors in the form of an "information request" (IR) letter when each discipline has finished its initial review of its section of the pending application.

I. DEFINITIONS AND EXPLANATION OF TERMS

1. The term "review and act on" is understood to mean the issuance of a complete action letter after the complete review of a filed complete application. The action letter, if it is not an approval, will set forth in detail the specific deficiencies and, where appropriate, the actions necessary to place the application in condition for approval.

2. A major amendment to an original application submitted within 3 months of the goal date extends the goal date by 3 months.

3. A resubmitted original application is a complete response to an action letter addressing all identified deficiencies.

4. Class 1 resubmitted applications are applications resubmitted after a complete response letter (or a not approvable or approvable letter) that include the following items only (or combinations of these items):

a. Final printed labeling.

b. Draft labeling.

c. Safety updates submitted in the same format, including tabulations, as the original safety submission with new data and changes highlighted (except when large amounts of new information including important new adverse experiences not previously reported with the product are presented in the resubmission).

d. Stability updates to support provisional or final dating periods.

e. Commitments to perform Phase 4 studies, including proposals for such studies.

f. Assay validation data.

g. Final release testing on the last 1–2 lots used to support approval.

h. A minor reanalysis of data previously submitted to the application (determined by the agency as fitting the class 1 category).

i. Other minor clarifying information (determined by the agency as fitting the class 1 category).

j. Other specific items may be added later as the Agency gains experience with the scheme and will be communicated via guidance documents to industry.

5. Class 2 resubmissions are resubmissions that include any other items, including any item that would require presentation to an advisory committee.

6. A Type A meeting is a meeting which is necessary for an otherwise stalled drug development program to proceed (a "critical path" meeting).

7. A Type B meeting is a (1) pre-IND, (2) end of Phase 1 (for Subpart E or Subpart H or similar products) or end of Phase 2/pre-Phase 3, or (3) a pre-NDA/PLA/BLA meeting. Each requestor should usually only request 1 each of these Type B meetings for each potential application (NDA/PLA/BLA) (or combination of closely related products, i.e., same active ingredient but different dosage forms being developed concurrently).

8. A Type C meeting is any other type of meeting.

TITLE VIII—MISCELLANEOUS

Clarification of seizure authority

There are two situations under which FDA-regulated products are imported into the United States and enter domestic commerce. The first occurs when the product passes FDA and Customs scrutiny at the border and is permitted entry into the country. The second is under section 801(d)(3), as added by the FDA Export Reform and Enhancement Act of 1996, which permits products to be imported into the United States solely for processing with the requirement that the finished product subsequently be exported. Section 803 amends the seizure provisions in section 304(d)(1) of the act to clarify that any person who seeks to export an article that has been imported under either of these conditions, pursuant to the export provisions in section 801(e) of the Act, must demonstrate that the article was intended for export at the time that it entered commerce. The clarification of section 304(d) applies only to seized and condemned imported articles and does not affect articles proffered for import that are refused entry under section 801(a) and properly exported within 90 days of refusal.

National uniformity for nonprescription drugs and cosmetics

The economic strength and vitality for consumer products in the United States rests upon the tradition of one vast nationwide marketplace, regulated by strong Federal and State agencies committed to protecting the public health. An essential element of a nationwide marketplace is a national uniform system of regulation. It is intended that the FDA provide national leadership in assuring the safety, effectiveness, and proper labeling and packaging for nonprescription drugs and cosmetics marketed throughout the country, under the Federal Food, Drug, and Cosmetic Act, the Poi-

son Prevention Packaging Act, and the Fair Packaging and Labeling Act.

Under our Federal system, it is important that State and local officials enforce the same regulatory requirements for products as do our Federal officials. Different or additional requirements as the State or local level can work against our national marketplace, confuse consumers, raise prices, undermine public confidence in our regulatory system and in products important to the public health, and result in divergent public health protection throughout the country.

Federal law currently provides strong public health protection for nonprescription drugs and cosmetics and their constituents. Nonprescription drugs are subject to careful and comprehensive regulation by the FDA. The conditions under which nonprescription drugs are considered safe and effective, for use by the lay consumer, are specified by FDA in nonprescription drug monographs or by new drug and antibiotic drug applications. FDA also ensures that the labeling of nonprescription drugs provides adequate directions for use, and adequate warnings against unsafe use, through these monographs and drug marketing applications, as well as through a number of general and specific labeling regulations. The FDA also has strong legal authority to regulate cosmetics. A cosmetic is considered adulterated if it contains a substance that may be injurious to users. The FDA has required that every cosmetic ingredient and every finished cosmetic product be substantiated for safety before it can be marketed. A cosmetic is misbranded if the safety of the product or an ingredient has not been established prior to marketing and that fact is not disclosed in a label warning. FDA also requires all ingredients to be declared on the label of cosmetics. For both nonprescription drugs and cosmetics, the FDA has clear statutory authority to require warnings or to ban unsafe ingredients. Use of any unsafe ingredient, or any false or misleading labeling, for a nonprescription drug or a cosmetic is unlawful and subject to regulatory action. The FDA authority in this area extends from manufacture through retail sale of these products.

Section 808 of the legislation therefore established a new section 761 of the Federal Food, Drug, and Cosmetic Act that adopts, as a general rule, the requirement of national uniformity in the regulation of nonprescription drugs and cosmetics and their constituents. No State or local government is permitted to impose different or additional requirements that relate to the subject matter covered by the three Federal laws as they apply to nonprescription drugs and cosmetics. These include requirements imposed on product manufacture or composition, labeling, advertising, or any other form of public notification or communication.

Under the legislation, all States may vigorously enforce requirements for nonprescription drugs and cosmetics that are identical to the Federal requirements, including the Federal prohibition against the adulteration or misbranding of these products. Most States have enacted laws regulating nonprescription drugs and cosmetics, based on the Federal laws, that prohibit the adulteration or misbranding of these products in the same terms as the Federal laws. These identical State requirements may be enforced by State officials, without first notifying the FDA or obtaining any Federal

approval, using compliance powers that are different from or in addition to the Federal compliance mechanisms, e.g., the power of a State to order an embargo or recall of a violative product or to impose civil penalties. States may also continue to use such traditional revenue measures as registration fees. Accordingly, one consistent national regulatory system will be implemented, relying upon both Federal and State enforcement, providing strengthened public health protection throughout the country.

There may occasionally be situations where a local problem could justify a different or additional regulatory requirement for nonprescription drugs or cosmetics in a particular State. The legislation therefore specifically authorizes States to petition for an exemption from the general rule of national uniformity under these circumstances. The FDA may grant an exemption if the State demonstrates that its proposed local requirement protects an important public interest that is not protected under the Federal laws, the local requirement would not cause any nonprescription drug or cosmetic to be in violation of any Federal law, and the local requirement would not unduly burden interstate commerce. State exemption petitions should be given a high priority by the FDA, and should be handled promptly upon receipt. Where the problem identified by a State could represent a national problem, on the other hand, the proper way for a State to proceed would be by petitioning the FDA to change the national requirements, using established agency procedures.

The legislation allows State officials to place a nonprescription drug on prescription only, to solve a local problem such as a localized outbreak of abuse of a product. Once the problem has abated, the drug can then be switched back to nonprescription status. Similarly, State laws will continue to apply to the practice of pharmacy, i.e., to the licensing, discipline, and professional duties of pharmacists. Accordingly, the legislation clearly recognizes and reflects the paramount need to protect the public health, both locally and nationally.

A State, locality, or person may continue to take advantage of their right to petition the FDA, where it has not issued a regulation, to make a certain requirement a national requirement, under the right supplied to them in 21 CFR 10.30, the citizen petition provision of the Code of Federal Regulations.

The FDA jurisdiction relating to dissemination of information about nonprescription drugs and cosmetics and their constituents applies to the label and labeling for these products. It is important that any State or local requirements imposed on industry relating to the advertising of nonprescription drugs or cosmetics, or to any other form of public notification or communication relating to these products and their constituents, be identical with the FDA requirements for the label and labeling of these products. Accordingly, the legislation extends national uniformity to the requirements for all forms of public information and public communication, not just to the label and labeling. The legislation, however, would not preclude State officials from issuing their own State warnings in accordance with local law. Similarly, voluntary programs such as the "Mr. Yuk" initiative sponsored by local Poison Control Centers will not be affected.

Under the legislation, national uniformity is provided for all of the types of requirements for nonprescription drugs and cosmetics and their constituents under State laws that are related to requirements included in the Federal laws, e.g., requirements to prevent adulteration or misbranding or other illegal marketing or to issue public notice about the safety of constituents. All forms of State requirements that affect these products are included within the general rule of national uniformity, whether they are specifically denominated as applying to nonprescription drugs and cosmetics or more broadly apply to unfair competition or to all chemicals, ingredients, or contaminants to which consumers and other members of the public are exposed. To the extent that any type of State law imposes a requirement for a warning or other type of public notification with respect to nonprescription drugs or cosmetics or any constituent, that requirement is prohibited unless such a requirement is prescribed under one of the three identified Federal laws and the State requirement is identical to the Federal requirement.

Finally, the legislation explicitly provides that it shall not be construed to modify or otherwise affect the traditional product liability law of any State. Tort liability rules and requirements would remain unchanged and unaffected.

The committee further notes the importance of nonprescription drugs in the nation's health care system. While consumers spend less than 2 cents of their health care dollar on nonprescription drugs, such drugs produce substantial savings to the individual and the health care system in reductions in physician visits, prescription drug costs, insurance costs, lost time from work, and travel. The committee notes that products switched from prescription to nonprescription status contribute significantly to these savings. For example, according to a study conducted by Kline & Company, consumer health care savings attributable to self-care with nonprescription medicines reached $20.6 billion in 1996. Kline calculated that medicines transferred from prescription to nonprescription status were responsible for $12.9 billion of the $20.6 billion savings. The savings are determined by calculating what consumers would be likely to spend if, instead of using nonprescription medicines, they were to see a doctor, purchase a prescription medicine and lose time from work.

The committee therefore expects that the FDA, as part of its mission set forth in section 101 of this legislation (i.e., "shall promptly and efficiently review clinical research and take appropriate action on the marketing of regulated products in a manner that does not unduly impede innovation or product availability") will establish appropriate procedures and policies, including performance standards, to expedite the review of applications to switch prescription drugs to nonprescription status. The committee encourages the FDA to give strong consideration to establishing a separate office for nonprescription drugs and conferring on that office primary review and sign-off authority for applications to switch drugs from prescription to nonprescription status. At a minimum, the committee recommends that an individual or individuals within the Center for Drug Evaluation and Research be designated to ensure timely and efficient agency review and action on such applications and that the agency consider using the explicit authority granted

to it to contract for outside expert review when such contracts would achieve more timely and efficient reviews."

Information program on clinical trials for serious or life-threatening diseases

Sec. 808 amends section 402 of the Public Health Services Act to establish a registry of clinical trials, both publicly or privately funded, of experimental drugs and biologicals for serious or life-threatening medical conditions. Registry information must be understandable to the general public and include the purpose of the experimental protocol, trial eligibility criteria, and sites and contact points for people wishing to enroll in a trial. Patients, health care providers, researchers and the public would access the registry through toll-free telephone communications and other information systems. Sec. 808 also requires the Secretary of HHS, within 2 years after enactment, to investigate and report on whether it is necessary or feasible to include medical device trials in the registry. The purpose of the registry is to simplify the process through which individuals with serious or life-threatening medical conditions obtain information about opportunities to participate in clinical trials of experimental therapies.

Pharmacy compounding

Section 809 of S. 830 is intended to clarify the application of the Federal Food, Drug and Cosmetic Act to the professional practice of pharmacist compounding of drug products. States currently have the authority to license pharmacists and regulate pharmacies, including the scope of pharmacy practice. All States include compounding as a core component of the profession of pharmacy. While the Food, Drug and Cosmetic Act specifically exempts pharmacies from inspection and registration provisions of the Act, it has been the contention of the Food and Drug Administration that compounded products are not exempt from the Act's new drug provisions. The committee has found that clarification is necessary to address current concerns and uncertainty about the Food and Drug Administration's regulatory authority over pharmacy compounding.

The committee has worked extensively with the Food and Drug Administration and other interested parties to reach consensus on how to ensure continued availability of compounded drug products as a component of individualized therapy, while limiting the scope of compounding so as to prevent small-scale manufacturing under the guise of compounding. Section 809 establishes parameters under which compounding is appropriate and lawful. This section is not intended to subvert the requirements that apply to investigational new drugs or to result in experimentation without appropriate human subject protections, including proper informed consent.

The views of the Committee with respect to certain subsections of Section 809 are outlined below:

The exemptions in section (h)(1) are limited to compounding for an individual patient based on the medical need of such patient for the particular drug compounded. To qualify for the exemptions, the pharmacist or physician must be able to cite a legitimate medical need for the compounded product that

would explain why a commercially available drug product would not be appropriate. Although recording the medical need directly on each prescription order would not be required, this technique would be one of many acceptable ways of documenting the medical need for each compounded drug product. This medical need would not include compounding drugs that are essentially copies of commercially available drug products for largely economic reasons. The pharmacist may rely on appropriately documented input from the physician as to whether a commercially available drug product is not appropriate for the identified individual patient.

Implementation of subsection (h)(1)(B)(I)(I)(bb), regarding bulk drug substances, is expected to coincide with the implementation of subsection (h)(3), except that compliance with the standards of an applicable United States Pharmacopeia monograph is not dependent on any further implementation under subsection (h)(3).

Among other requirements, a bulk drug substance used for compounding must have been manufactured in an establishment that has registered under section 510 of the Act. In addition to applying to domestic manufacturing establishments, this requirement shall also apply to foreign establishments, once the requirement in section 801 of this Act, which requires foreign establishments to register and list under section 510 of the Act, becomes effective.

In compliance with subsection (h)(1)(B)(I)(III), pharmacists may retain each certificate of analysis until the supply of such bulk drug substance has been exhausted, and must record in the compounding record the manufacturer, repackager (if any), and the lot number of the bulk drug substance.

The list published pursuant to subsection (h)(1)(B)(iv) includes drug products that have been withdrawn or removed from the market because the finished drug product and/or a component thereof has been found to be unsafe or not effective. The Federal Register document that includes the list should briefly describe the basis for the withdrawal or removal and provide interested parties with an opportunity to comment. The list should not include products that have been withdrawn or removed solely because of manufacturing issues.

Interested parties should be allowed to petition, under 21 CFR § 10.30, to change the listing of a particular drug product under subsection (h)(1)(B)(v) should research and technology yield advances which correct the compounding difficulties.

Regarding subsection (h)(2)(B), until the State agency of jurisdiction in which the pharmacy is located enters into a memorandum of understanding (MOU) with the Secretary or 180 days after the development of the standard MOU, whichever comes first, the exemption shall not apply if inordinate quantities of compounded products are distributed outside of the State in which the compounding pharmacy or physician is located. "Inordinate" quantities means amounts typically associated with ordinary commercial drug manufacturing.

As required under subsection (h)(3), the Secretary will be required to promulgate regulations limiting compounding to drug

substances that are components of drug products approved by the Secretary and to other drug substances as the Secretary may identify. It is expected that the Secretary's regulations would allow compounding with drug products, or the components of drug products, that are lawfully distributed, including drug products that are not new drugs under 21 U.S.C. § 321(p) and drug substances that authorized for use under an effective Investigational New Drug application (IND) protocol under 21 U.S.C. § 355(I) and 21 CFR Part 312. The FDA may, in development of the list for other substances approved for compounding, consult with pharmacy organizations and other interested parties, beyond the United States Pharmacopeia.

V. COST ESTIMATE

U.S. CONGRESS,
CONGRESSIONAL BUDGET OFFICE,
Washington, DC, June 27, 1997.

Hon. JAMES M. JEFFORDS,
Chairman, Committee on Labor and Human Resources, United States Senate, Washington, DC.

DEAR MR. CHAIRMAN: The Congressional Budget Office has prepared the enclosed cost estimate for S. 830, the Food and Drug Administration Modernization and Accountability Act of 1997.

If you wish further details on this estimate, we will be pleased to provide them. The CBO staff contact is Anne Hunt.

Sincerely,

JUNE E. O'NEILL, *Director.*

S. 830—Food and Drug Administration Modernization and Accountability Act of 1997

Summary: S. 830 would reauthorize the Prescription Drug User Fee Act (PDUFA) of 1992, which empowers the Food and Drug Administration (FDA) to collect user fees from the pharmaceutical industry. The user fee program would be reauthorized, with some modifications, for an additional five years. The bill would also amend the Food, Drug and Cosmetic Act (FD&CA) and the Public Health Service Act to reform the FDA's regulatory and approval processes for drugs, biological products, devices, foods and animal drugs. One provision would grant a six-month extension of market exclusivity for pharmaceutical manufacturers who conduct pediatric studies on select prescription drugs.

CBO estimates that enacting S. 830 would result in net additional discretionary spending of $63 million in 1998 and $445 million over the 1998–2002 period, assuming appropriation of the authorized amounts. Reauthorizing the user fee program would yield $601 million in offsetting collections over five years; these amounts would also be authorized to be spent, subject to appropriation. Extending market exclusivity for certain drugs would increase direct spending by $65 million over the 1998–2002 period.

By preempting state and local laws that regulate nonprescription drugs differently than federal law, S. 830 would impose an intergovernmental mandate as defined in the Unfunded Mandates Reform Act (UMRA). CBO estimates that compliance with this man-

date would result in no significant costs for state and local governments.

Estimated cost to the Federal Government: The estimated budgetary impact of S. 830 is shown in the following table. For the purposes of this estimate, CBO assumes that all amounts authorized in the bill would be appropriated by the start of each fiscal year and that outlays would follow the historical spending patterns for the FDA. The costs of this legislation fall within budget function 550 (Health).

[By fiscal year, in millions of dollars]

	1997	1998	1999	2000	2001	2002
SPENDING SUBJECT TO APPROPRIATION						
Spending Under Current Law						
Estimated Authorizations:						
Authorization Level	887	919	949	982	1,016	1,050
Estimated Outlays	895	914	937	971	1,005	1,038
Collection of User Fees:						
Authorization Level	−101	0	0	0	0	0
Estimated Outlays	−101	0	0	0	0	0
Spending of User Fees:						
Authorization Level	101	0	0	0	0	0
Estimated Outlays	100	26	5	0	0	0
Proposed Changes						
Estimated Authorizations:						
Authorization Level	0	63	93	102	90	97
Estimated Outlays	0	38	61	80	83	93
Collection of User Fees:						
Authorization Level	0	−110	−116	−119	−128	−128
Estimated Outlays	0	−110	−116	−119	−128	−128
Spending of User Fees:						
Authorization Level	0	110	116	119	128	128
Estimated Outlays	0	104	114	118	126	128
SPENDING SUBJECT TO APPROPRIATION						
Spending Under S. 830						
Estimated Authorizations:						
Authorization Level [1]	887	982	1,042	1,084	1,106	1,147
Estimated Outlays	895	952	998	1,051	1,088	1,131
Collection of User Fees:						
Authorization Level [1]	−101	−110	−116	−119	−128	−128
Estimated Outlays	−101	−110	−116	−119	−128	−128
Spending of User Fees:						
Authorization Level [1]	101	110	116	119	128	128
Estimated Outlays	100	130	119	118	126	128
DIRECT SPENDING						
Direct Spending:						
Estimated Budget Authority	0	0	7	18	28	11
Estimated Outlays	0	0	7	18	28	11

[1] The 1997 level is the amount appropriated for that year.

BASIS OF ESTIMATE

Estimated authorizations: In addition to reauthorizing the user fee program, the bill would reform the FDA's approval and regulatory processes with the intent of accelerating product approvals and alleviating regulatory requirements. It would require the FDA to comply with statutory deadlines for reviewing new products. S. 830 would require the FDA, in coordination with the National Institutes of Health (NIH) and the Centers for Disease Control (CDC), to establish a program to provide information on treatment, detection, and prevention of serious diseases and on clinical trials

currently studying these conditions. Other provisions would result in small budgetary savings.

Enforced Deadlines for FDA Action on Submissions. The bill would require the Secretary to develop and publish in the Federal Register a plan bringing the FDA into compliance with the obligations and deadlines contained in the FD&CA and other relevant statutes. Among other objectives, the plan must bring the FDA into full compliance with the statutory review deadlines in the FD&CA by July 1, 1999. The plan must also ensure that the FDA eliminate any backlog of submissions by January 1, 2000. The agency would also be required to implement the FD&CA inspection and postmarket monitoring requirements by July 1, 1999.

Assuming that the volume and quality standards for reviews were to remain constant, the FDA would require additional staff and resources to reduce review times significantly and eliminate the backlog of product submissions. Because S. 830 would somewhat relax current FDA regulations, the number of product applications could increase, placing further demands on the agency's resources. CBO estimates that the additional personnel and resources necessary to meet the proposed deadlines would exceed any savings realized through regulatory relief offered by S. 830. This provision would cost the federal government an estimated $50 million in 1998 and $267 million over five years.

Information Program on Clinical Trials. S. 830 would require the Director of the National Institutes of Health in coordination with the FDA and the Centers for Disease Control to establish a program to provide information on treatment, detection, and prevention of serious diseases and on clinical trials currently studying these conditions. This program would include establishing a database of all federally and privately funded clinical trials and a toll-free telephone information line available to health care providers, researchers, individuals with serious diseases, and all other members of the public.

The NIH already has such a program for clinical trials that it funds for cancer, AIDS, and rare diseases. Privately funded clinical trials are also included in these databases on a voluntary basis. The FDA would be able to disclose information on clinical trials, and NIH would be required to expand its current database significantly to accommodate the increase in volume of trials and information. After the system was set up, additional maintenance costs would be incurred to keep up with the status and results of clinical trials, and with new protocols on treatment and prevention of serious diseases and conditions. Costs would also arise to operate a telephone information line staffed by health professionals.

CBO based its estimate on the cost of maintaining the current data banks and information networks, the estimated portion of clinical trials currently contained in NIH's databases, and conversations with professionals experienced in this area. CBO assumes that it would take two years to create a system that would meet the minimum requirements specified in the bill, at a cost of $20 million in 1998 and $45 million in 1999. For each year thereafter, CBO estimated a cost of $50 million for maintenance and quality improvement. Costs would total $215 million over the 1998–2002 period.

Third-Party Review of Applications. The FDA would be required to accredit independent entities and individuals to review and make initial classification recommendations on section 510(k) device submissions. Devices that are life-sustaining or supporting, intended for implantation for more than one year, or designated as class III devices under section 515 would be exempted from this provision, except at the agency's discretion. The FDA would also have the discretion to allow accredited entities and individuals review premarket approval (PMA) applications for class III devices. Compensation arrangements for these reviews would be made between the sponsor and the reviewer. CBO estimates that this proposal would save approximately $1 million over five years.

Reclassification of Class III Devices. S. 830 would amend the FDA's current practice of automatically designating as class III products new devices that are not substantially equivalent to a legally marketed predicate device. Sponsors of devices designated as class III could request the FDA to classify their device as a class I or II device, and could make a recommendation about the classification. The FDA would have 60 days to make a final determination on a sponsor's recommendation. This provision would reduce the number of premarket applications reviewed by the FDA, saving $1 million in 1998 and $12 million over five years.

Reporting Product Changes to the FDA. The bill would waive the requirement that manufacturers file an additional application for an investigational device exemption for minor changes in the intended use or design of an investigational device. Minor changes are those that would not affect the efficacy or safety of the device. CBO estimates that this provision would save approximately $11 million over five years.

User fees

The bill would reauthorize current prescription drug user fees through September 30, 2002. The current authorization expires at the end of fiscal year 1997. The bill would also authorize new fees to be levied on manufacturers and suppliers of food contact substances. Proceeds from these fees would be available for spending, subject to appropriation.

Reauthorization of the Prescription Drug User Fee Act of 1992. As with current law, the reauthorized program would levy three types of user fees on pharmaceutical manufacturers: application and supplement fees, establishment fees, and product fees. Aggregate amounts of such fees are specified in the bill for each of fiscal years 1998–2002; these amounts would be adjusted to reflect cumulative inflation since 1997. CBO's estimate assumes that the inflation adjustment would apply to the specified authorization, not to the prior year's actual authorization. Under the proposal, the FDA would make annual adjustments so that the total revenues collected for establishment and product fees would equal those for application and supplement fees. The amounts collected are authorized to be spent, subject to appropriation. CBO estimates that the FDA would collect $110 million in 1998 and $601 million over five years.

Any fees collected in excess of the amount specified in the appropriations act for a given year would be credited to the FDA appro-

priations account and subtracted from the amount of fees authorized for the following year. The FDA could not assess the user fees unless appropriations for FDA salaries and expenses, excluding any user fees, were at least equal to appropriations for 1997, adjusted for inflation.

Fees for Food Contact Substances. The bill would include food contact substances among the items regulated under the FD&CA. Food contact substance could be used only if the FDA issued, and the food contact substance met, standards for the use of such additives. Alternatively, manufacturers or suppliers could give the FDA advance notification that the intended use of their food contact substance was safe according to agency regulations. Unless the FDA determined that the food contact substance was unsafe within 120 days of this notice, the notification would become effective.

The Secretary could authorize a fee, based on the resources needed to process these notifications, to be collected from individuals submitting notifications. The fee would be available to the FDA until expended, without fiscal year limitation. Although CBO cannot determine the amount of such fees, the provision would have no net budgetary impact, because the fees would be set to cover the agency's costs for reviewing and processing food contact substance notifications.

Direct spending

The bill would grant an additional six months of market exclusivity to pharmaceutical manufacturers that conduct pediatric studies on select drugs. This provision would affect direct spending because it would increase costs for the Medicaid rebate program and the Federal Employees Health Benefit Program (FEHBP). This provision would apply to pediatric studies commenced before January 1, 2004.

The Secretary of Health and Human Services, through the Commissioner of the FDA, would issue a list of drugs for which additional pediatric information might yield a health benefit.

If manufacturers of targeted drugs submitted pediatric studies to the FDA, their product would receive an additional six months of market exclusivity. This benefit would accrue to both approved drugs and those awaiting approval. Manufacturers of an approved drug that received an extension under this provision could, if eligible, receive an additional six months of exclusivity for a supplemental application.

By extending the market exclusivity of certain drugs, this proposal would increase prescription drug costs for Medicaid, FEHBP, Veterans Affairs (VA) facilities, the Department of Defense, and the Public Health Service for the six months of the extension. In the absence of this provision, these programs may have had access to less expensive generic products. In the case of Medicaid and FEHBP, the additional costs of this provision would represent direct spending. At this time, the costs to FEHBP, the VA, the Department of Defense, and the Public Health Service cannot be determined. CBO estimates that this provision would have no net budgetary effect in 1998 but would increase federal outlays for Medicaid by $65 million over the 1998–2002 period.

Pay-as-you-go considerations: The Balanced Budget and Emergency Deficit Control Act of 1985 set up pay-as-you-go procedures for legislation affecting direct spending or receipts through 1998. CBO estimates that enactment of S. 830 would have no significant effect on direct spending or receipts in 1998.

VI. Regulatory Impact Statement

Estimated impact on State, local, and tribal governments: By preempting state and local laws that regulate nonprescription drugs differently than federal law, S. 830 would impose an intergovernmental mandate as defined in UMRA. CBO estimates that compliance with this mandate would result in no significant costs for state and local governments. Consequently, the threshold established in UMRA ($50 million in 1996, adjusted annually for inflation) would not be exceeded. This mandate would not affect tribal governments.

By granting certain drug manufacturers a six-month extension of market exclusivity for their products, the bill would make prescription drugs provided under Medicaid more expensive. CBO estimates that states' share of these costs would total about $28 million over the next five years. This provision would not constitute a mandate under UMRA because prescription drugs under Medicaid are provided at a state's option.

Estimated impact on the private sector: S. 830 would impose some new private-sector mandates and would replace some existing mandates with new, less burdensome requirements. In addition, the bill would reauthorize application fees and certain other fees paid by pharmaceutical companies. However, since these fees do not become effective until Congress appropriates them, they do not constitute a private-sector mandate. Thus, the direct cost of all private-sector mandates in this bill are minimal, and the total effect could be a net reduction in mandated costs imposed on the private sector.

Sections 803 and 808 would impose new mandates on the private sector. Section 803 would change the definition of when a food, drug, device, or cosmetic intended for export is not deemed to be adulterated or misbranded in situations in which exportation is made to the original foreign supplier. This section also would impose a new mandate on persons seeking to export a condemned imported article by imposing a new certification requirement. Section 808 would direct the Secretary to establish "a data bank of information on clinical trials for drugs, and biologicals, for serious or life-threatening diseases and conditions." This provision would impose a new mandate on sponsors of such clinical trials by requiring them to forward to the data bank information about eligibility criteria for participation in the trial, the location of the trial, and a point of contact within 21 days after the clinical trial is approved by FDA. CBO estimates that the costs of these mandates would be minimal.

Several new mandates would cost no more and perhaps less than the current regulatory requirements that they would replace. Section 601 would require manufacturers of medical devices to submit a written notice, rather than a supplemental application as currently required, for certain types of manufacturing changes. Section

619 would set new quality standards specifically for positron emission tomography drugs, but relieve them of the new drug application process (required under section 505 of the Food Drug and Cosmetic Act) and certain other regulations. Section 610 would establish a single licensing requirement for biological products that would replace current licensing requirements.

Estimate prepared by: Federal cost: Anne Hunt (FDA) and Cyndi Dudzinski (NIH); impact on State, local, and tribal governments: John Patterson; and impact on the private sector: Anna Cook.

Estimate approved by: Paul N. Van de Water, Assistant Director for Budget Analysis.

VII. SECTION-BY-SECTION ANALYSIS

Sec. 1. Short Title.

Section 1 provides that the act be cited as the "Food and Drug Administration Modernization and Accountability Act of 1997."

Sec. 2. Table of Contents.

Section 2 contains the table of contents.

Sec. 3. References.

Section 3 states that whenever this Act provides for amendment to, or repeal of, a section or other provision, the referenced section or provision is of the Federal Food, Drug, and Cosmetic Act (FFDCA; 21 U.S.C. 321 et seq.)

TITLE I—IMPROVING PATIENT ACCESS

Sec. 101. Mission of the Food and Drug Administration.

Section 101 amends FFDCA section 903 (21 U.S.C. 393) by redesignating subsections (b) and (c) as subsections (c) and (d) and adding IN GENERAL that the Administration shall protect the public health by ensuring that foods are safe, wholesome, and sanitary; human and veterinary drugs are safe and effective; there is a reasonable assurance of safety and effectiveness of devices intended for human use; cosmetics are safe and properly labeled; and the public health and safety are protected from electronic product radiation, and (2) SPECIAL RULES that require the Administration promptly and efficiently review clinical research and take appropriate action on the marketing of regulated products in a manner that does not unduly impede innovation or product availability. Further, the Administration shall participate with other countries to reduce the burden of regulation, to harmonize regulatory requirements, and to achieve appropriate reciprocal arrangements.

Sec. 102. Expedited Access to Investigative Therapies.

Section 102 amends Chapter V (21 U.S.C. 351 et seq.) to add a new subchapter.

SUBCHAPTER D—UNAPPROVED THERAPIES AND DIAGNOSTICS

Sec. 551. Expanded Access to Unapproved Therapies and Diagnostics.

Section 102 of this Act creates a new section 551 of the FFDCA. Section 551(a) allows any person, acting through a state licensed physician, to request from manufacturers a product that is under investigation for the Food and Drug Administration's (FDA) approval for the diagnosis, monitoring, or treatment of a serious disease or condition or any other disease or condition designated by the Secretary as appropriate for access to such products. Expanded access is conditional on whether (1) a licensed physician determines that the person has no comparable or satisfactory alternative therapy; (2) the licensed physician determines that the risk to the patient from the investigational product is not greater than that of the risk from the disease or condition; (3) the Secretary determines that an investigational drug (IND) or investigational device (IDE) application complies with regulations governing these applications; (4) the Secretary determines that the manufacturer is diligently pursuing an approval; and (5) the Secretary decides that expanded access to an investigational product will not prevent adequate patient enrollment for ongoing clinical trials for the unapproved product. There is also to be a determination by FDA that there is sufficient evidence of safety and effectiveness such that the investigational product can be used in his manner.

Section 551(b) allows a sponsor to submit one or more protocols for expanded access for an investigational product. The protocols may include any use of the drug or device outside a clinical investigation prior to approval for marketing, including treatment use, single patient use, emergency use, and uncontrolled trials. The Secretary may waive certain requirements for expanded access to investigational new products for use by a single patient only in an emergency when times does not permit an application to be filed for an exemption. The Secretary can authorize shipment and use of the product in advance of any submission.

Section 551(c) allows the Secretary to inform national, state, and local medical associations and societies, and other appropriate organizations and persons about the availability of the investigational drugs or devices under expanded access protocols. However, this does not apply to protocols for single patient use. Sec. 551(d) allows the Secretary at any time to stop expanded access if the drugs or devices do not meet the requirements set forth in this section.

Sec. 103. Expanded Humanitarian Use of Devices.

Section 103 amends section 520(m) (21 U.S.C 360j(m)) (Humanitarian Device Exemption section) formalizing requests for exemption from device efficacy studies intended for patient populations of less than 4,000. Requests would now be in the form of an application that the Secretary must approve or deny within 60 days. This section amends section 520(m)(4)(B) to allow a physician, if he had not received a timely response from a hospital institutional review committee (IRC) to which the physician had applied for an exemption, to use the device if the patient would suffer harm or death

waiting for IRC approval. The physician will then be required to inform the chairperson of the IRC of such a use on a particular patient, the date used, and why it was necessary. New section 520(m)(5) allows the Secretary to require a recipient of an exemption to demonstrate continued compliance with requirements if the Secretary deems this necessary to protect the public health or believes that the criteria for the exemption are no longer met.

TITLE II—INCREASING ACCESS TO EXPERTISE AND RESOURCES

Sec. 201. Interagency Collaboration.

Section 201 amends section 903(b) (21 U.S.C 393(b)) of the FFDCA to require that the Secretary create programs to foster collaboration among science-based federal agencies such as the National Institutes of Health (NIH) and others to enhance the scientific and technical expertise available to product reviewers. This expertise will be available for review activities for medical therapies such as the development, clinical investigation, evaluation, and postmarket monitoring of emerging therapies. It will also cover complementary therapies and advances in nutrition and food science.

Sec. 202. Sense of the Committee Regarding Mutual Recognition Agreements and Global Harmonization Efforts.

Section 202 gives the sense of the Senate Committee on Labor and Human Resources that the Secretary should consult with the Secretary of Commerce and support the Office of the U.S. Trade Representative in moving toward acceptance of mutual recognition agreements (MRAs) with the European Union. These MRAs will cover the regulation of drugs, biological products, devices, foods, food additives, and color additives as well as good manufacturing practices. The Secretary should regularly participate in meetings with other foreign governments to harmonize regulatory requirements. The Committee also would like to ensure that the Department of Health and Human Services, Office of International Relations (established in section 803 of the FFDCA) continuously works towards harmonizing international regulatory requirements.

Sec. 203. Contracts for Expert Review.

Section 203 amends Chapter IX (21 U.S.C 391 et seq.) by adding a new section on contracts for expert review. Under new section 906, the Secretary will be authorized to enter into contracts with qualified nongovernmental individuals or organizations to make recommendations to the Secretary on any applications or submissions for approval or classification under FFDCA or under section 351(a) of the Public Health Service Act (42 U.S.C 262(a)) for biological products. All such contracts will be subject to requirements under section 708 of the FFDCA relating to confidentiality of information.

The Secretary shall use this authority to enter into contracts with individuals or organizations to review applications or submissions whenever the Secretary determines that such reviews will improve the timeliness or quality of the application under review. The official at the FDA who is responsible for the matter that the con-

tractor is reviewing must make final decisions on the contractors' recommendations within 60 days. The Secretary shall retain authority to approve or disapprove submissions for a product, or to classify an article as a device under section 513(f)(1).

Sec. 204. Accredited-Party Participation.

Section 204 amends Subchapter A of Chapter V (21 U.S.C. 351 et seq.) of the FFDCA to establish new section 523—Accredited-Party Participation. This section requires the Secretary to accredit nongovernmental individuals or entities to make recommendations for initial classification of and to review premarket notification for medical devices. Devices that are long-term implantable, life-sustaining, or life-supporting will be excluded from accredited-party review.

Under subsection 523 of the new law, the Secretary will have discretion to accredit nongovernmental groups or parties to (a) review premarket notification reports for devices (under section 510(k)) and make recommendations for their initial classification, or (b) to review premarket approval applications (under section 515) and make recommendations for their approval or disapproval.

Within 180 days of enactment, the Secretary must establish the accreditation process for third-party medical device review. The accreditation process must be published in the Federal Register. If an accredited party fails to comply with duties published by the Secretary, such as avoidance of conflicts of interest or protection of confidential information, the Secretary may, after giving notice and opportunity for a hearing, suspend or withdraw program accreditation from that party.

Device sponsors who are considering filing a premarket notification or a premarket approval application, as described in subsection (2), will be given the option of selecting an accredited entity. Upon request, the Secretary must provide the device sponsor with a minimum of two accredited parties from which to choose. Compensation must be arranged between the sponsor and the accredited party.

The Secretary must require accredited parties to submit their recommendations and supporting rationale in writing. For initial classification of a device, the Secretary must make a final decision within 30 days of receiving the recommendation. For premarket approval applications, the Secretary will have authority to change recommendations that an accredited party proposes, and must provide the party submitting the application or report with a written explanation of the reasons for the change.

The program for third-party accreditation is authorized to operate for a period of either five years following the date on which at least two accredited parties are available to review devices "in each of at least 70 percent of generic types of devices required for review under subsection (a)"; or, four years after the date on which the Secretary notifies Congress that the Secretary has acted upon at least 35 percent of the devices under subsection (a) for classification or review, whichever occurs first.

Within one year of enactment, the Secretary must contract with an independent research organization to prepare and submit a written report examining the use of accredited-parties to review no-

tifications of and applications for medical devices. The Secretary must submit the report to Congress no later than six months from the date when the accredited program concludes. The report must contain a description of the benefits or detriments to public health of using accredited parties to conduct those reviews. The report must contain a summary of all relevant data, including review times, compensation, and recommendations made by the accredited party and the Secretary.

Sec. 205. Device Performance Standards.

Section 205 amends section 514 (21 U.S.C. 360(d)) of the FFDCA by adding a new section for "Recognition of a Standard." Section 205 authorizes the Secretary to recognize in the Federal Register nationally or internationally recognized standards. Such standards may be used to meet requirements for premarket submissions or other requirements of the Act. If a regulated person uses a recognized standard then that person must provide the Secretary with a declaration of conformity certifying that the device conforms with the recognized standard. When the recognized standard is no longer appropriate for satisfying requirements under the Act, the Secretary may withdraw recognition of that standard.

The Secretary must accept self-declarations from sponsors that a device conforms with a recognized standard unless the Secretary finds that (a) the data submitted to support conformity is not consistent with the standard identified in the self-declaration of conformity, or (b) the standard identified in the declaration of conformity does not apply to the device under review. The Secretary may request a device sponsor to submit the data that was relied on to make a self-declaration of conformity. Device sponsors who make self-declarations of conformity for a recognized standard must maintain data and information that supports conformity of the device to the standard for a period of two years after the date of classification or approval of the device, or for a period equal to the life expectancy of the device, whichever is longer.

Section 301 (21 U.S.C. 331) will be amended to prohibit the falsification of a declaration of conformity or the failure or refusal to provide data or information that the Secretary may request under new section 514(c)(3).

Section 501 (21 U.S.C. 351(c)) will be amended to reflect a new condition under which a device is adulterated. A device would be adulterated if it is falsely declared to be in conformity with recognized performance standards under section 514(c).

TITLE III—IMPROVING COLLABORATION AND COMMUNICATIONS

Sec. 301. Collaborative Determination of Device Data Requirements.

Section 301 amends section 513(a)(3) (21 U.S.C. 360c(a)(3)) of the FFDCA. Upon written request from a device sponsor, the Secretary will be required to meet to determine the type of scientific evidence that is necessary to demonstrate the effectiveness of a device. It is proposed that such meetings between the Secretary and device sponsors take place before clinical trials begin or before an investigation device exemption is filed. Within 30 days after the meeting, the Secretary must specify the type of scientific evidence the

sponsor will need to support the proposed use of the device. For any clinical data that the Secretary may require, the Secretary must provide a written specification to the device sponsor that reflects the Secretary's view that such data are necessary to establish the effectiveness of the device, and that a less burdensome means is not available. The Secretary's specification for scientific evidence will be binding upon the Secretary, unless he finds that (a) it is not in the interest of the public health to modify the specification, or (b) scientific evidence obtained during consideration of an investigational device exemption makes the specification inappropriate.

Sec. 302. Collaborative Review Process.

Section 302 amends section 515(d) (21 U.S.C. 360e(d)) of the FFDCA. Within 100 days of receiving a complete premarket approval application (PMA), the Secretary will be required to meet the device sponsor to discuss the status of review, if so requested in writing. If the PMA does not appear in a form that will require an approval, the Secretary must indicate in writing before the meeting any deficiencies that the device sponsor must correct and information the device sponsor must provide to bring the application to an approvable form. The Secretary and the device sponsor may mutually agree on a different meeting schedule.

TITLE IV—IMPROVING CERTAINTY AND CLARITY OF RULES

Sec. 401. Policy Statements.

Section 401 amends current section 701 (General Authority) (21 U.S.C. 371(a)). After a two year evaluation period, the Secretary, by February 27, 1999, a recently issued guidance document for "Good Guidance Practices" (62 Federal Register 8961) into a regulation.

Sec. 402. Product Classification.

Section 402 amends chapter VII (21 U.S.C. 371 et seq.) of the Act to add a new "Subchapter D—Review of Applications and Environmental Impact Reviews." Under new section 741, a product sponsor for a drug, biological product, or device may submit certain recommendations to the Secretary along with an application for premarket review. Those recommendations may call for a classification determination as well as a center-specific review. The Secretary will have a total of 60 days to (a) classify the product, or (b) assign it to a center for review, and (c) inform the sponsor of the reasons for the Secretary's decisions. The Secretary will be bound by these decisions except for public health reasons or with the written consent of the sponsor. If the Secretary does not make a decision within 60 days, the sponsor's recommendations for classification or assignment will be final.

Sec. 403. Use of Data Relating to Premarket Approval.

Section 403 amends current section 520(h)(4) (21 U.S.C. 360j(h)(4)). The Secretary is authorized to use data from a premarket approval application six years after an application is approved for the purpose of facilitating reclassification and/or approval of applications submitted by other device sponsors for the

same kind of device. The publicly available detailed safety and effectiveness summaries required to be submitted for premarket approval shall be available for use by the Secretary as the evidentiary basis for any action based on the data.

Sec. 404. Consideration of Labeling Claims for Product Review.

Section 404 amends section 515(d)(1)(a) (21 U.S.C. 360e(d)(1)(A)) and section 513(i)(1) for labeling claims for premarket approval applications under premarket notifications. In making determinations to approve or deny an application, the Secretary will be required to limit the evaluation of safety and effectiveness to those uses proposed in the product label if it is determined that the labeling is neither false nor misleading. For products claiming substantial equivalence with others having different technological characteristics, the Secretary will be required to request only that information that is necessary and corresponds to the least burdensome means of demonstration. The Secretary must also base this finding only on the intended uses in the proposed labeling in a report submitted under section 510(k).

Sec. 405. Definition of a Day for Purposes of Product Review.

Section 405 amends section 201 (21 U.S.C. 321). A calendar day is described as one in which the Secretary has responsibility to review a new product. Any day during which a product sponsor for a drug, device, biological product, new animal drug, color additive, or food additive is responding to Secretary requests for information from the Secretary will be excluded. A reference to a date relating to the receipt of filing of such an application means the date when the Secretary receives or files, as appropriate, a complete application.

Sec. 406. Certainty of Review Timeframes.

Section 406 amends section 510(k) (21 U.S.C. 360) to state that the Secretary must review premarket notifications within 90 days. This new requirement will conform with current practice in reporting on review timeframes for 510(k) submissions. This section will also amend section 515(d) (21 U.S.C. 360e(d)) to ensure that the Secretary must review applications within 180 days even if the application is amended.

Sec. 407. Limitations on Initial Classification Determinations.

Section 407 amends section 510 (21 U.S.C. 360). The Secretary will be prohibited from the current practice of withholding the initial classification of a device because of a failure of a manufacturer to comply with any provision of the FFDCA unrelated to making a determination of substantial equivalence, including good manufacturing practice regulations.

Sec. 408. Clarification of General and Specific Uses of A Device For Purposes of Substantial Equivalence.

Section 408 will require issuance of a new regulation. Within 270 days of enactment, the Secretary must promulgate final regulations establishing criteria that will be considered when evaluating claims for substantial equivalence under section 513(f)(1) (21 U.S.C.

360(f)(1)). The Secretary must develop criteria to determine when the specific intended use of a device is not reasonably included within its general use.

Sec. 409. Clarification of the Number of Required Clinical Investigations.

Section 409 amends current sections 505(d) (21 U.S.C. 355(d)) and 513(a)(3)(A) (21 U.S.C. 360c(a)(3)(A)) adding a new sentence to 505(d) giving the Secretary discretion to approve drugs under certain conditions on the basis of one adequate and well-controlled investigation with confirmatory evidence, and by changing "clinical investigations" in 513(3)(a) to "1 or more clinical investigations."

Sec. 410. Prohibited Acts.

Section 410 will repeal section 310(1) (21 U.S.C. 331(l)) of current law. The section of the FFDCA that prohibits manufacturers from making truthful statement of facts about Secretary-approved products will be repealed.

TITLE V—IMPROVING ACCOUNTABILITY

Sec. 501. Agency Plan for Statutory Compliance and Annual Report.

Section 501 amends Section 903(b) (21 U.S.C. 393(b)) of the FFDCA to create two new subsections 903(b)(4) Agency Plan for Statutory Compliance and 903(b)(5) Annual Report. The Committee does not intend to duplicate any requirement of current law that applies under the Government Performance and Results Act (GPRA) [P.L. 103–62].

New section 903(b)(4) will require that the Secretary, not later than 180 days after enactment, develop a plan to bring the Secretary into compliance with each of the FFDCA's obligations. The plan will be developed after consultation with experts, health care professionals, representatives of patients and consumer advocacy groups, and regulated industries. The plan must be published in the Federal Register and will be reviewed biannually by the Secretary for revisions as necessary. The plan's objectives will be to (i) minimize deaths and injuries suffered by persons who may use products regulated under the FFDCA; (ii) maximize the clarity and availability of information about the product review process and new products for potential consumers and patients; (iii) implement all inspection and post-market monitoring provisions of the Act by July 1, 1999; (iv) ensure access to the scientific and technical expertise necessary to properly review products; (v) establish a schedule to bring the "Administration" into compliance by July 1, 1999 with the product review times in the Act for products submitted after the date of enactment of this section; and (vi) eliminate the backlog of products awaiting final action by January 1, 2000.

New section 930(b)(5)(A) will require that the Secretary solicit public comment by publishing in the Federal Register an annual report that would: (i) contain statistical information on the performance of the Secretary to assist Congress in assessing his performance; (ii) compare the Secretary's performance in that year to the plan and Secretary's statutory obligations; (iii) analyze any failure to achieve any element of the agency plan; (iv) identify any reg-

ulatory policy that has a significant impact on compliance with any objective of the agency plan or any statutory obligation; and (v) set forth any proposed revision to any such regulatory policy, or objective of the plan, that has not been met.

New section 903(b)(5)(B) will require that the information given annually will include statistics on all applications and submissions made under the FFDCA and approved or subject to final action by the Secretary during that year. The statistical information will consider the date of: (1) the submission of any investigational application; (ii) the application of any clinical hold; (iii) the number of applications submitted for approval or clearance; (iv) the acceptance for filing of any application; (v) the occurrence of any unapprovable action; (vi) the occurrence of any approvable action; and (vii) the approval or clearance of any application or submission described in (iii).

TITLE VI—BETTER ALLOCATION OF RESOURCES BY SETTING PRIORITIES

Sec. 601. Minor Modifications.

Section 601 amends Section 520(g) (21 U.S.C. 360j(g)) of the FFDCA to require the Secretary, within 120 days of enactment, to issue new regulations modifying parts 812 and 813 of Title 21, Code of Federal Regulations, updating procedures and conditions for granting exemptions, and governing, when the manufacturer of a device, which is the subject of an approved investigational device exemption, may make minor modifications to that device without restarting the clinical trial or submitting a supplement to the investigational device exemption in effect for the clinical trial.

The new regulations must permit developmental changes in devices (including manufacturing changes) in response to information collected during the investigation, without requiring an additional investigational device exemption approval or the approval of a supplement, as long as the sponsor determines, prior to making the changes, that they will not affect the soundness of the investigational plan or the rights, safety, or welfare of the human subjects involved. Also, the changes must not constitute a significant change in the design or basic operational principles of the device. In reviewing an application, FDA is required to accept and review data or information to determine whether there is a reasonable assurance of safety and effectiveness of the device if: (I) the data or information are derived from investigations of a previously approved device, the device has been modified during or after the investigations, and the modification does not constitute a significant change in the device's design or basic operational principles; or (II) the data or information relating to the device are available for use under the Act, and are relevant to the design and intended use of the device subject to the pending application.

Supplemental applications will be required for any changes to a marketed device that affect safety and efficacy. This will not be required if the change is a modification in a manufacturing method or procedure and the holder of the application submits a written notice describing the change in detail, summarizing the data or information supporting the change, and informing the Secretary that, despite the change, the manufacturer is still in compliance with the

FDA's good manufacturing practices (GMP) regulations. Holders of approved applications who submit manufacturing change notifications may not distribute their products until 14 days after the Secretary has been notified.

When reviewing a supplement to an approved application for an incremental change to the design of a device that affects safety or effectiveness, the Secretary must approve the supplement if nonclinical data show that the modification creates the intended additional capacity, function, or performance of the device, and the clinical data from the approved application, and any of its supplements, provide a reasonable assurance of safety and efficacy.

Sec. 602. Environmental Impact Review.

Section 602 amends Chapter VII (21 U.S.C. 371) of the FFDCA, adding new section 742 dealing with environmental impact reviews. The section establishes that no action taken by the Secretary under this law shall be subject to an environmental impact assessment, an environmental impact statement, or other environmental consideration unless the Secretary demonstrates, in writing, that (1) there is a reasonable probability that the environmental impact of the action is substantial and within the factors the Secretary is authorized to consider, and (2) that consideration of the impact will directly affect the decision on the action.

Sec. 603. Exemption of Certain Class Devices From Premarket Notification Requirement.

Section 603 amends Section 510(k) (21 U.S.C. 360(k)) of the FFDCA, establishing that all Class I devices, except those that are intended for a use that is of substantial importance in preventing impairment of human health, or present a potential unreasonable risk of illness or injury, are exempted from pre-market review. The FDA's enforcement powers and good manufacturing practices will still apply to these devices. In addition, the Secretary must, no later than 30 days after enactment, publish a list of each type of Class II device that does not require pre-market review. One day after the list is published, a class II device, based on the Secretary's initiative or upon the petition of an interested person, may be exempted from the pre-market notification requirement. The petition, or the Secretary's intent to exempt such a device, must be published in the Federal Register and allow for a 30 day public comment period. Within 120 days of the Federal Register notice, an order must be published setting forth the Secretary's final determination about the device's exemption.

Sec. 604. Evaluation of Automatic Class III Designation.

Section 604 amends Section 513(f) (21 U.S.C. 360c(f)) of the FFDCA to establish that any device manufacturer who submits a report under section 510(k) for review of a type of device that has not been previously classified under the Act, and which is classified into Class III, may request, within 30 days of receiving the notification, that the Secretary classify the device into either Class I or II. In the request, the manufacturer may recommend to the Secretary the device's classification. The request must include a description

of the device, and detailed information and reasons for its reclassification.

Not later than 60 days after a classification request, the Secretary, by written order, must classify the device. This classification will be the initial classification of the device, and any device classified into Class I or II shall be a predicate device for determining substantial equivalence. Any device that remains in class III will be deemed adulterated until it is either approved under section 515 or exempted from such approval under section 520(g). Once an order classifying a device is issued, the Secretary must, within 30 days, publish its announcement in the Federal Register.

Sec. 605. Discretion To Track Devices.

Section 605 amends Section 519(e) (21 U.S.C. 360i(c)) of the FFDCA, establishing that any patient who receives a device, subject to tracking under this section, may refuse to release, or refuse permission to release, their name, address, social security number, or other identifying information used for tracking purposes. Within 180 days of enactment, the Secretary must develop and publish in the Federal Register a list identifying devices that require tracking under the Act. Devices not identified by the Secretary will be considered exempt from mandatory tracking. The Secretary will have the authority to modify the list of devices exempt from the mandatory tracking.

Sec. 606. Secretary's Discretion To Require Postmarket Surveillance.

Section 606 amends Section 522 (21 U.S.C. 3601) of the FFDCA, establishing certain limitations on FDA's post-market surveillance authority for devices. This section stipulates that each device manufacturer, required to conduct post-market surveillance must, within 30 days of receiving a notice that surveillance is required, submit a surveillance plan for the Secretary's approval. Within 60 days of receipt of the plan, the Secretary must determine if the person who is to conduct the surveillance is qualified and experienced and whether the plan will result in the collection of useful data that can reveal unforeseen adverse events necessary to protect the public health and provide additional safety and effectiveness information.

The Secretary may not approve the plan until it has been reviewed by a scientifically qualified review committee, which the Secretary is authorized to select. Manufacturers will be required to conduct surveillance for no more than 24 months. However, if the Secretary determines that additional surveillance is necessary to further explore unforeseen adverse events documented during the initial surveillance, the time period may be extended, and the person conducting the surveillance will be given an opportunity for an informal hearing to determine whether the additional surveillance time is appropriate.

Sec. 607. Reporting.

Section 607 amends Section 519 (21 U.S.C. 360i) of the FFDCA, repealing certain reporting requirements for device distributors. However, it establishes that regulations shall require distributors, including importers, to keep records and make them available to

the Secretary upon request. In addition, the provision adds new language to section 510 of the FFDCA (Registration of producers of Drugs and Devices) that will exempt wholesale distributors of devices, who do not manufacturer, repackage, process, or relabel, from the Act's registration requirements.

Sec. 608. Pilot and Small-Scale Manufacture.

Section 608 amends Section 505(c) (21 U.S.C. 355(c)) of the FFDCA to establish that a new drug manufactured in a pilot or small facility may be used to demonstrate the drug's safety and effectiveness and to obtain its approval prior to scaling up to a larger facility. The Secretary retains the authority to determine whether a full scale production facility is necessary to ensure the drug's safety and effectiveness.

Sec. 609. Requirements For Radiopharmaceuticals.

Section 609 requires the Secretary, within 180 days of enactment, and after consultation with patient advocacy groups, associations, physicians licensed to use radiopharmaceuticals, and the regulated industry, to issue proposed regulations governing the approval of radiopharmaceuticals designed for diagnosis and monitoring of diseases and conditions. The regulations must provide that the product's safety and effectiveness, governed under section 505 of the FFDCA and section 351 of the Public Health Service Act, must include (but not be limited to) consideration of the product's proposed use in the practice of medicine, the product's pharmacological and toxicological activity (including any carrier or ligand of the radiopharmaceutical), and the product's estimated absorbed radiation dose.

Within 18 months of enactment, the Secretary must issue final regulations governing the approval of radiopharmaceuticals. This section establishes a "SPECIAL RULE" stating that in the case of a radiopharmaceutical intended to be used for diagnostic or monitoring purposes, its approved marketing indications may, in appropriate situations, refer to manifestations of disease (such as biochemical, physiological, anatomic, or pathological processes) common to or present in one or more disease states. The term "radiopharmaceutical" is defined to mean an article: (A) intended for use in the diagnosis or monitoring of a disease or a manifestation of a disease in humans; and (B) which exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons; or any nonradioactive reagent kit or nuclide generator which is intended to be used in its preparation.

Sec. 610. Modernization of Regulation of Biological Products.

Section 610 amends section 351(a) of the Public Health Service Act (PHSA) (42 U.S.C. 262(a)), to codify the regulation of biological products. It states that a biological product may not be introduced into interstate commerce unless (A) the product has a biologics license; and (B) the package is marked with the product's name, the manufacturer's name, address, and license number, and the product's expiration date. By regulation, the Secretary must establish requirements for the approval, suspension, and revocation of biologics licenses. A license will be approved based on a demonstration

that the biological product is safe, pure, and potent, and that the facility where the product is manufactured, processed, packed, or held meets standards to assure its continued safety, purity, and potency. Also, the application will be approved only on the condition that the licensee agrees to permit inspection of its production facility. The Secretary must prescribe certain licensing and labeling exemptions for products undergoing investigation.

The section amends section 351 of the PHSA eliminating the requirement that biologics manufacturers obtain establishment licenses, and redefines biological product to mean: "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, analogous product, or arsphenamine or its derivatives (or any other trivalent organic arsenic compound) applicable to the prevention, treatment, or cure of diseases or conditions of human beings."

In addition, the section establishes a "SPECIAL RULE" directing the Secretary to take steps necessary to minimize differences in the review and approval of products required to have both a biologic license application under section 351 of the PHSA and a new drug application (NDA) under section 505(b)(1) of the FFDCA.

Sec. 611. Approval of Supplemental Applications for Approved Products.

This section states that within 180 days of enactment, the Secretary must publish in the Federal Register performance standards for the prompt review of supplemental applications for drugs previously approved under the Act. Within this same timeframe, the Secretary must also issue final guidance to clarify the requirements and facilitate the submission of data to support the approval of the supplemental application. The guidance must: (1) clarify the circumstances that will permit published material to qualify as the basis for approval; (2) specify data requirements that will avoid duplication by recognizing the availability of data previously submitted; and (3) define supplemental applications that are eligible for priority review.

The Secretary must designate someone in each FDA Center (except the Center for Food Safety and Applied Nutrition) who will be responsible for encouraging prompt review of supplemental applications, and who will work with sponsors to facilitate the development of and data to support supplemental applications. In addition, the Secretary must implement programs and policies that will foster collaboration between FDA, NIH, professional medical and scientific societies, and others to identify published and unpublished studies that could support a supplemental application. Moreover, the Secretary must encourage sponsors to submit supplemental applications or conduct further research based on these studies.

Sec. 612. Health Care Economic Information.

Section 612 amends Section 502 (21 U.S.C. 352) of the FFDCA, which specifies the circumstances whereby drugs and devices may be deemed "misbranded," by adding language to deal with pharmacoeconomic health care claims. It establishes that a drug or device, about which a health care economic statement may be included in its labeling or advertising submitted to a formulary com-

mittee, managed care organization, or similar entity with drug selection responsibilities, will be considered misbranded if the economic statement is not based on "competent and reliable" scientific evidence.

The bill states that any such economic statements will be subject to section 502 only, and defines "health care economic statement" as "any statement that identifies, measures, or compares the costs (direct, indirect, or intangible) and health care consequences of a drug to another drug or to another health care intervention for the same indication, or to no intervention, where the primary endpoint is an economic outcome."

Sec. 613. Expediting Study and Approval of Fast Track Drugs.

Section 613 amends Chapter V (21 U.S.C. 351) of the FFDCA, establishing a new Section 561 under new Subchapter E—Fast Track Drugs. The bill states that the Secretary will facilitate development and expedite approval of new drugs and biological products, to be known as "fast track drugs," that are intended for treating serious and life-threatening conditions and show potential to address unmet medical needs. Drug sponsors may request that the Secretary designate drugs for fast track consideration, and the designation may be made concurrently with, or at any time after, the submission of the investigation application. Within 30 days of the request, the Secretary will determine if the drug meets the fast track criteria, and if so, will designate the drug and take action to expedite its development and review.

The Secretary may approve a fast track drug based on a determination that the drug has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. Such an approval may obligate the manufacturer to (i) conduct post-approval studies to validate the surrogate endpoint and confirm its clinical benefit; and (ii) submit copies of all promotional materials related to the fast tack drug during the preapproval review period and, following approval, at least 30 days prior to the dissemination of the materials for such a time as the Secretary finds appropriate.

The approval of a fast track drug may be withdrawn using expedited procedures, including an opportunity for informal hearing, if the sponsor fails to diligently conduct the post-approval studies; a post-approval study fails to verify a clinical benefit; other evidence demonstrates that the drug is not safe or effective under its conditions of use; or the manufacturer disseminates false for misleading promotional materials.

This provision also provides for the review of incomplete applications for the approval of fast track drugs. If early evaluation of clinical data for a fast track drug shows evidence of effectiveness, the Secretary will evaluate for filing and may commence review of portions of an application if the sponsor provides a schedule for submitting the information necessary for a complete application and any required user fee. In situations where the fast track drug's application is incomplete, the time periods for review of human drug applications agreed to in section 736 [drug user fee authority] will not apply until a completed application is submitted.

The Secretary must develop and widely distribute to physicians, patient organizations, pharmaceutical and biotechnology compa-

nies, a comprehensive description of the provisions applicable to fast track drugs, and establish an ongoing program to encourage the development of surrogate endpoints that are reasonably likely to predict clinical benefit. Within 1 year of enactment the Secretary must issue guidance that describes the EPA's policies and procedures required to implement this provision.

Sec. 614. Manufacturing Changes For Drugs and Biologics.

Section 614 amends Chapter VII (21 U.S.C. 371) of the FFDCA, establishing new Section 751 under new Subchapter E—Manufacturing Changes. It describes the types of manufacturing changes the manufacturer of a new drug or biologic may make under the Act.

Before distributing a new drug or biologic made after a change in the manufacturing process established in its original application, the sponsor must validate the effect of the change on the product's identity, strength, quality, purity, and potency—as they may relate to its safety and effectiveness. Changes needing validation must be reported to the Secretary, and the manufacturer may distribute the drug after a change is made as follows: (A) Major manufacturing changes, determined by the Secretary to have a substantial potential to adversely affect identity, strength, quality, purity, and potency as they may relate to safety and effectiveness, must be submitted in a supplemental application. Drugs made after these changes may not be distributed until the Secretary approves the supplement. Major manufacturing changes means: (1) changes in the qualificative or quantitive formulation or specifications; (2) changes the Secretary determines require an appropriate human study; and (3) changes which the Secretary determines have a substantial potential to have an adverse effect on the drug's safety or effectiveness; (B) As determined by the Secretary, manufacturing changes other than major changes, can be made at any time and must be reported annually with supporting data, or be reported in a supplemental application. Drugs having undergone a minor manufacturing change may be distributed 30 days after the Secretary receives a supplemental application, unless the applicant is notified that prior approval of the supplement is required. After notification to the applicant, the Secretary must approve or disapprove each supplement. The bill proposes a "SPECIAL RULE" that allows the Secretary to determine the types of manufacturing changes after which distribution of the drug may begin when the supplement is submitted. A period for transition from prior requirements is defined.

Sec. 615. Data Requirements for Drugs and Biologics.

Section 615 requires the Secretary through the Commissioner of FDA, within 1 year of enactment, to issue guidance that describes when manufacturers will be permitted to submit certain abbreviated study reports instead of traditional full reports with their new drug applications (NDAs). The guidance must describe when abbreviated reports are appropriate and what their format should be.

Sec. 616. Food Contact Substances.

Section 617(a) amends Section 409(a) of the FFDCA (21 U.S.C. 348(a)) by providing that a food additive that is a food contact substance is unsafe unless it is used in conformity with an applicable food additive regulation or an effective premarket notification. This section further amends Section 409(a) to state that a food is not adulterated by virtue of containing or bearing a food additive that is a food contact substance used in accordance with an applicable regulation or effective notification. Section 617(a) establishes a new process, premarket notification, by which food contact substances can lawfully enter the marketplace.

Section 617(b) creates a new Section 409(h) of the FFDCA. A new Section (h)(1) establishes the process, terms, and conditions of the PMN approach for food contact substances. Receipt by FDA of the PMN is required at least 120 days prior to introduction of the substance into interstate commerce or its delivery for such introduction. The notification must provide notice of the identity and intended use of the substance and other information that forms the basis of the notifier's determination that the intended use of the food contact substance is safe. The standard for safety for food contact substances incorporates the standard under current law, specifically Section 409(c)(3)(A) of the FFDCA (21 U.S.C. 348(c)(3)(A)). Section (h)(1) also authorizes FDA to issue regulations specifying the information required in a PMN. The types and amount of information required will be comparable to that currently required for food additive petitions for "indirect additives."

A new Section (h)(2) created by Section 617(b) of this bill specifies that a PMN becomes effective automatically 120 days after receipt by FDA, unless FDA objects. FDA is not required to publish a notice of filing in the Federal Register as it currently does in response to food additive petitions. Thus, the time period for consideration of a PMN runs from the fier has not demonstrated in the PMN that the food contact substance is safe. FDA is required to notify the submitter of this determination, and it is expected that this notice will specify the basis for the determination insufficient detail to establish that the Agency has not been arbitrary or capricious. Section (h)(2) also establishes that FDA's decision to object to a PMN is final agency action subject to immediate judicial review. Finally, the Section specifies that a notification is only effective with respect to the specific substance listed in the notification, and does not extend to similar or identical substances manufactured by a person other than the manufacturer listed in the notification.

Section (h)(3) created by Section 617(b) of the bill mandates that the PMN process be utilized for authorizing the marketing of a food contact substance unless FDA determines that a food additive petition is necessary to provide adequate assurance of safety, or unless FDA and a company agree that a petition may be submitted. FDA is authorized to issue regulations to identify the circumstances under which petitions will be required, and the Committee fully expects that such regulations will be based on sound scientific considerations reasonably related to public health and safety, such as probable consumption levels and potential toxicity. It is intended

that the PMN process will be the primary method for authorizing the marketing of food contact substances.

Section (h)(4) created by Section 617(b) requires FDA to keep all information in the PMN confidential for the duration of the 120 day review period. Following this period, the contents of the PMN would be available for disclosure to the public as are safety and functionality data filed in a food additive petition, consistent with the Freedom of Information Act (FOIA) and other related disclosure statutes.

Section reasonable fees from those who file a PMN in order to assure that FDA has the resources needed to review the PMN within 120 days. These fees must be based on the resources necessary to process the PMNs, including reasonable administrative costs. FDA is directed by the bill to conduct a study of the costs of administering the PMN program, and, on the basis of this study, issue regulations within 18 months of enactment establishing the amount of the fee for a PMN. The fees must only reflect the actual costs of processing the PMNs, and must be set at a level that is not unduly burdensome on industry. These fees will be credited to the FDA, and will be used by the Agency solely to defray the costs of administering the PMN program.

Section (h)(6) provides the new definition of "food contact substance" to be added to the FFDCA. The definition of food contact substance includes any substance intended for use as a material or a component of materials used in manufacturing, packing, packaging, transporting, or holding food if such use is not intended to have any technical effect in such food. This definition includes some substances that do not meet the definition of a food additive because, for example, such substances are generally recognized as safe or prior sanctioned for their uses, or they are not reasonably expected to become a component of food. "Not reasonably expected to become a component of food" has been interpreted by FDA to include food contact substances separated from food by a barrier to migration and those processing aids (e.g., solvents and catalysts) that by virtue of the conditions of manufacture are removed from the final food contact substance. A premarket notification is permitted for food contact substances that are not food additives, but is required only for those food contact substances that also meet the definition of a food additive.

Section 617(b)(3) of this bill adds authorization for FDA to issue regulations establision demonstrates that just as Congress recognized the need for a process for revoking a regulation for a food additive, the situation is no different for food contact substances being marketed subject to a PMN.

Section 617(c) specifies that this legislation shall be effective following 18 months from the date of its enactment. PMNs may be filed after this period (and become effective 120 days after their receipt by FDA) without regard to whether FDA has issued regulations implementing this legislation.

Sec. 617. Health Claims for Food Products.

Section 617 amends section 403(r)(3) (21 U.S.C. 343(r)(3)) of the FFDCA. It provides an alternative to the current standard and review process by allowing health claims to be made based on infor-

mation published by authoritative U.S. government scientific bodies. The new provision will allow a health claim in food labeling without FDA authorization, if it consists of or will otherwise summarize or reflect information contained in a publication of a Federal Government scientific organization or some component of the National Academy of Sciences. If any such health claim is made, it must be submitted to FDA, along with the published information on which it is based, at least 120 days prior to its appearance in the marketplace. A claim meeting the requirements may be made until a final regulation, prohibiting or modifying the claim, becomes effective, or a U.S. District Court determines that the nutritional claims requirements have not been met.

Sec. 618. Pediatric Studies Marketing Exclusivity.

Section 618 amends Chapter V (21 U.S.C. 351 et seq.) of the FFDCA by creating new section 515A—Pediatric Studies of Drugs. If, prior to the approval of a new drug, the Secretary determines that information about the drug will produce health benefits in a pediatric population, and makes a written request for pediatric studies, and the studies are completed and accepted, then the sponsor or manufacturer can qualify for up to 6 months of extra market exclusivity. If the Secretary makes a written request for pediatric studies of an already marketed drug, and those studies are completed, then the manufacturer can be granted up to 6 months of increased market exclusivity as well.

Within 180 days of enactment, the Secretary, after consultation with experts, must develop and publish an initial list of approved drugs for which additional pediatric information may produce health benefits. When the Secretary has formally requested pediatric studies those studies must be conducted by a written protocol agreed to by the sponsor, patent holder, and the Secretary. Less than 60 days after the pediatric studies have been submitted, the Secretary must determine whether the studies were done properly and notify the sponsor or holder. In addition, the provision contains a section describing other means by which the study protocol requirements can be met.

This section contains a sunset provision that states that no market exclusivity will be granted based on pediatric studies begun after January 1, 2004. In addition, the Secretary must complete a study and report to Congress no later than January 1, 2003, the agency's experience under the program. The report must address the program's effectiveness, the adequacy of its incentives, the program's economic impact, and any suggestions for the program's modification.

Sec. 619. Positron Emission Tomography

Section 619 amends the FFDCA to include the regulation of compounded positron emission tomography (PET) drugs. The provision defines compounded PET drugs to mean drugs that exhibit spontaneous disintegration of unstable nuclei; includes nonradioactive reagents, nuclide generators, accelerators, electronic synthesizers, or associated software used to prepare any such drug; and, which have been compounded in accordance with State law by or on the order of a practitioner licensed in that State or in a fed-

eral facility in accordance with the laws of the State in which it is located. The Act is amended to stipulate that a compounded PET drug is adulterated, and thus subject to regulatory and/or legal action by FDA if it is not compounded, processed, packed, or held in accordance with the PET compounding standards and official monographs of the United States Pharmacopoeia (USP).

The act is further amended to provide that neither a New Drug Application (NDA) nor an Abbreviated New Drug Application (ANDA) is required by a licensed practitioner to produce a compounded PET product in accordance with USP standards. Within 30 days of enactment, the Secretary must publish in the Federal Register a notice revoking all previously published efforts by FDA to provide industry guidance and regulatory standards for PET products.

TITLE VII—FEES RELATING TO DRUGS

Sec. 701. Short Title.

Section 701 provides that this title be cited as the "Prescription Drug Users Fee Reauthorization Act of 1997."

Sec. 702. Findings.

Section 702 sets forth four congressional findings: (1) the prompt approval of safe and effective new drugs and other therapies is critical to improve public health; (2) additional resources augmenting the Food and Drug Administration's (FDA) review of human drug applications serve the public health; (3) the successful Prescription Drug User Fee Act of 1992 (PDUFA) program reduced drug review times; therefore it should be reauthorized for an additional 5 years and should be carried out by FDA with more ambitious and comprehensive regulatory goals; (4) fees authorized by amendments will be used to expedite the drug development and application review process through goals identified in letters [date unspecified] from the Secretary to the Chairman of the House Committee on Commerce and Chairman of the Senate Committee on Labor and Human Resources, as set forth in the Congressional Record [date unspecified].

Sec. 703. Definitions.

Section 703 augments several definitions in section 735 (21 U.S.C. 379(g)). New section 735 will not allow PDUFA funds to pay for review or processing of biological license applications for further manufacturing only nor cover a product that is not sod commercially and whose application or supplement is submitted by a State or Federal government entity. PDUFA would cover review of licenses for large volume biological products used for single dose intravenous injection or infusion. Section 703(3) amends section 735(4) to ensure that the term "final dosage form" of a prescription drug does not need any further "substantial" modification. Section 735(7) is amended to allow expenses of contractors of FDA to be paid with PDUFA funds. The "adjustment factor" would now be the lower of either the Consumer Price Index for all urban consumers (with August 1992 replaced with April 1997) or one plus the total percentage increase for a fiscal year since 1997 in the general

schedule of base pay for federal employees after adjustments have been made for employees stationed in the District of Columbia. The term "business affiliate" means a business relationship in which one business, directly or indirectly, controls or has the power to control, the other businesses, or a third party controls, or has the power to control both businesses.

Sec. 704. Authority to Assess and Use Drug Fees.

Section 704(a) amends Section 736(a) (21 U.S.C. 379h(a)) establishing types of fees. PDUFA re-authorization will begin in fiscal year (FY) 1998. It will require payment of fees whenever an application or supplement is submitted to the agency. Section 736(a)(1)(D) is amended to allow 75 percent of the fee to be refunded if FDA refuses to file an application.

Section 704(2) also adds three exceptions to the payment of fees. Section 736(a)(1) exempts in new subsection (E) an application or supplement for designated orphan drugs or indications submitted under section 526 to treat a rare disease or condition. To get an exemption, the application or supplement cannot include any uses other than for rare diseases or conditions. Section 736(a)(1) is amended to add a new subsection (F) wherein a person submitting an application for a pediatric drug will be assessed a fee only if the application is for the initial approval for use in a pediatric population or for use by pediatric and non-pediatric populations. Section 736(a)(1) is amended to add subsection (G) to refund a fee if the application is withdrawn. It allows the Secretary sole discretion to waive and refund a fee if no substantial work was performed on the application or supplement before it was withdrawn.

Section 704(3) also amends section 736(a)(2), the prescription drug establishment fee, to ensure that generic drug manufacturing establishments, whether they produce drugs that were approved before or after 1984 will not pay a fee nor will establishments that manufacture generic antibiotics.

Section 704(4) amends section 736(a)(3), the prescription drug product fee, to expand the definition of those who must pay the fee. It will require all applicants be included whose product has been submitted for listing with the Secretary. It also amends the schedule for payment so that a fee will be paid for the fiscal year in which the product is first submitted for listing under section 510 of the FFDCA (Registration of Producers of Drugs and Devices) or for relisting if the product had been withdrawn. After the fee is paid for the fiscal year, the fee must be paid on or before January 31 of each year thereafter. Innovator antibiotic drug products (antibiotic drugs whose initial certification or approval was under section 507) are subject to product fees; however, generic antibiotic drug products with approval granted prior to the Drug Price Competition and Patent Term Restoration Act of 1984.

Section 704(b) amends section 736(b) relating to fee amounts (21 U.S.C. 379h(b)) to eliminate the word "schedule" and set the fee to be assessed as follows: (1)(A) FULL FEES. The application fee shall be $250,704 in FY 1998, $256,338 in FY 1999 and 2000, $267,606 in FY 2001, and $258,451 in FY 2002. (1)(B) PARTIAL FEES. The supplement fee shall be $125,352 in FY 1998, $128,169 in FY 1999 and 2000, $133,803 in FY 2001, and $129,226 in FY 2002.

Section 736(b)(2) will also amend fee revenue amounts to be collected from establishment fees. Total fee revenues collected as establishment fees shall be $35.6 million in FY 1998, $36.4 million in FY 1999 and 2000, $38 million in FY 2001, and $36.7 million in FY 2002.

Section 736(b)(3) will also amend fee revenue amounts to be collected from product fees. Total revenues collected from product fees for a fiscal year shall equal total establishment fees each year.

Section 736(c) is amended to create a section entitled "Adjustments," with a new subsection title "(1) Inflation Adjustment." The Secretary could change the adjustment made each fiscal year to the fees collected by adding, on a compounded basis, the sum of all adjustments made each fiscal year after FY 1997. The annual fee adjustment should begin on September 30, 1997, and the establishment and product fees should be adjusted so that their revenue shall be set to equal the revenues collected from application and supplement fees.

Section 736(d) on fee waiver and reduction (21 U.S.C. 379h(d)) restructures the paragraphs and adds to the assessment provision that if the applicant is a small business and submits its first new drug application to the Secretary for review, it can receive a waiver or reduction in fees. Section 736g(d)(3)(A) defines the term "small business" to mean an entity that has fewer than 500 employees, including employees of affiliates. Section 736g(d)(3)(B) allows the Secretary to waive the fee if the small business or affiliate is submitting for the first time an application for approval of a human drug. After this first time waiver is granted, the small business or affiliate must pay fees on all subsequent applications or supplements. The Secretary may also use "standard costs" in making the finding that the waiver or fee reduction is necessary to protect the public health.

Section 704(e) amends section 736(f)(1) (21 U.S.C. 379g(f)(1)) to update to FY 1997. Section 704(f) amends section 736(g) (21 USC 379g(g)) to allow the transfer of appropriated funds from the account for salaries and expenses of one fiscal year to another fiscal year account if the funds are available solely for reviewing human drug applications. It also amends the statute to allow funds to be collected in each fiscal year in an amount specified in appropriation Acts or otherwise be made available for obligation. It also specifies that fees shall only be collected and be available to defray increases in the costs of the resources allocated for the review process for human drugs over such costs, excluding costs paid for fees collected under this section, for FY 1997; and multiplied by the adjustment factor.

Section 704(f) amends section 736(g)(3) and authorizes to be appropriated for fees: (A) $106,800,000 for FY 1998; (B) and (C) $109,200,000 for FY 1999 and 2000; (D) $114,000,000 for FY 2001; and (E) $110,100,000 for FY 2002. These amounts reflect adjustments in the total fee revenues made under this section and changes in the total funds collected by the four fees: application, supplement, establishment, and product fees.

Section 704(f)(3) amends section 736(g) to add a new section: (f)(4) OFFSET. This subsection allows any collected fees over the authorized amount to be credited to an appropriation account of

the FDA and be subtracted from the subsequent fiscal year authorization to collect fees.

Section 704(g) amends section 736 (21 U.S.C. 379h) to create a subsection (i) and provides that, to qualify for consideration of a waiver or fee reduction or refund, a person must submit a written request to the Secretary for this action within 180 days after the fee is due.

Section 704(h) amends section 736 (21 U.S.C. 379h) to create a subsection (h) providing for a special rule for waiver, refunds, and exceptions. It allows that any requests for waivers, refunds, or exceptions for fees paid prior to the date of enactment could be submitted in writing to the Secretary within one year after enactment of this Act.

Sec. 705. Annual Report.

Section 705 requires two reports to be prepared by the Secretary of Health and Human Resources and submitted to the House Committee on Commerce and the Senate Committee on Labor and Human Resources. The first will report, within 60 days after the end of the fiscal year, on the progress FDA achieved in meeting the performance goals identified in the letters described in section 702(4). The second will report within 120 days on the implementation of the authority for such fees during the fiscal year and FDA's use of the fees.

TITLE VIII. MISCELLANEOUS

Sec. 801. Registration of Foreign Establishments.

Section 801 amends section 510(i) of the FFDCA to require that any establishment within any foreign country engaged in the manufacture, preparation, propagation, compounding, or processing of a drug or a device that is imported or offered for import into the United States must register with the Secretary the name and place of business of the establishment and its United States' agent. The establishment must provide the information required under section 510(j) of the FFDCA. Section 801 authorizes the Secretary to enter into cooperative agreements with foreign countries to ensure that adequate and effective means are available to determine whether drugs or devices manufactured, prepared, propagated, compounded, or processed by a foreign establishment, if imported or offered for import into the U.S., should be refused admission on grounds set forth in section 801(a) of the FFDCA, i.e., imports and exports.

Sec. 802. Elimination of Certain Labeling Requirements.

Section 802 amends section 503(b)(4) of the FFDCA and provides that a drug subject to section 503(b)(1) is misbranded if at any time prior to dispensing the label of the drug does not bear, at a minimum, the symbol "Rx only." A drug that does not fall under (b)(1) is deemed to be misbranded if at any time prior to dispensing the label of the drug bears the symbol "Rx only." Also, section 502(d) of the FFDCA is repealed, i.e., labeling on habit forming narcotic or hypnotic drugs.

Sec. 803. Clarification of Seizure Authority.

Section 803 amends section 304(d)(1) of the FFDCA by removing the reference to paragraphs (1) and (2) of section 801(e)(1) of the FFDCA and inserting a reference to only subparagraphs (A) and (B) of section 801(e)(1) of the FFDCA. While the current provision appears to make inapplicable all of paragraphs (1) and (2) to the situation where a condemned article is exported to the original foreign supplier, the amending language makes inapplicable only two requirements found in subparagraphs (A) and (B). Additionally, this section adds the new sentence which provides that any person seeking to export an imported article under section 304(d) of the FFDCA must establish that the article was intended for export at the time the article entered commerce.

Sec. 804. Intramural Research Training Award Program.

Section 804 amends Chapter IX of the FFDCA [Miscellaneous], by adding the new section 907 [sic] which establishes the "Research Training Award Program." New subsection (a) authorizes the Secretary, acting through the Commissioner, directly or through grants, contracts, or cooperative agreements, to conduct and support research training in regulatory scientific programs by pre- and postdoctoral scientists and physicians. This may include support through the use of fellowships. New subsection (b) provides that the recipient of a fellowship may not be an employee of the Federal government. And, under new subsection (c), the Secretary is authorized, acting through the Commissioner, to support the provision of assistance for fellowships through a Cooperative Research and Development Agreement.

Sec. 805. Device Samples.

Section 805(a)(1) amends section 518(e)(2) of the FFDCA [Recall authority for devices] adding the new subsection (e)(2)(C) which provides that if the Secretary issues an amended order under subparagraph (A), he may require the person subject to the order to submit such samples of the device and its components as the Secretary may reasonably require. If the submission of the samples is impracticable or unduly burdensome, this requirement may be met by submitting complete information concerning the location of one or more such devices readily available for examination and testing. Section 805(a)(2) of the bill amends section 518(e)(2)(A) of the FFDCA by providing a technical amendment which strikes an apparently erroneous reference to subparagraph (C) in (e)(2)(A).

Section 805(b) [Records and reports on devices] amends section 519(a) of the FFDCA, as amended by section 607(a) of the bill, and adds new paragraph (a)(9) which provides that regulations issued under the first sentence of subsection (a) may reasonably require a manufacturer, importer, or distributor to submit samples of a device or its components that may have caused or contributed to a death or serious injury. This submission is not required if it is impracticable or unduly burdensome. The requirement may be met by the submission of complete information concerning the location of one or more such devices readily available for examination and testing.

Sec. 806. Interstate Commerce.

Section 806 amends section 709 of the FEDCA by providing that in any action to enforce the FFDCA respecting a device, food, drug, or cosmetic, the connection with interstate commerce required for jurisdiction shall be presumed to exist.

Sec. 807. National Uniformity for Nonprescription Drugs and Cosmetics.

(Amendment offered by Senator Gregg.) (This section was number 808 in amendments to the bill.)

Section 807 amends Chapter VII [General Authority] of the FFDCA, as amended by section 615 of the bill, by adding a new subchapter F entitled "National Uniformity for Nonprescription Drugs for Human Use and Cosmetics." New section 761(a) provides that, except in certain subsections, no State or political subdivision of a State may establish or continue to effect any requirement (1) that relates to the regulation of a drug intended for human use that is not subject to the requirements of section 503(b)(1) or a cosmetic and (2) that is different from or in addition to a requirement of this Act, the Poison Prevention Packaging Act, or the Fair Packaging and Labeling Act.

However, upon application by the State, the Secretary may, by regulation, after notice and opportunity for written and oral views, exempt a State requirement that protects an important public interest that will otherwise be unprotected; will not cause any drug or cosmetic to be in violation of any applicable requirement or prohibition under Federal law; and, will not unduly burden interstate commerce. This provision shall not include any requirement that relates to the practice of pharmacy or any requirement that a drug be dispensed only upon the prescription of a practitioner licensed by law to administer the drug. Furthermore, with regard to scope, this provision shall include any requirement relating to public information or any public communication relating to the safety and effectiveness of a drug or cosmetic. Any, nothing in this section shall be construed to modify or otherwise affect any action or the liability of any person under the product liability law of any State.

Sec. 808. Information Program on Clinical Trials for Serious or Life-Threatening Diseases.

(Amendment offered by Senator Dodd) (This section was number 808 in amendments.)

Section 808 amends section 402 of the Public Health Service Act (42 U.S.C. § 282; Director of National Institutes of Health) by inserting a new subsection 282(j), after redesignating subsection (j) as (k) and subsection (k) as (l). The new subsection provides that the Secretary, acting through the Director of NIH and subject to available appropriations, shall establish, maintain, and operate a program with respect to information on research relating to the treatment, detection, and prevention of serious or life-threatening diseases and conditions. The program shall, with respect to the agencies of HHS, be integrated and coordinated and, to the extent practicable, coordinated with other information banks.

After consulting with the Commissioner, the directors of the institutes of NIH, including the National Library of Medicine, and

the Director of the CDC, the Secretary shall establish a data bank of information on clinical trials for drugs, and biologicals, for serious or life-threatening diseases and conditions. The Secretary shall collect, catalog, store and disseminate this information through information systems, which must include toll-free telephone communications and be available to persons with serious or life-threatening diseases and conditions, the public, health care providers an researchers.

The Data Bank must include: (A) a registry of clinical trials of experimental treatments for serious or life-threatening diseases or condition that describes the purpose of each experimental drug or biological protocol, either with the consent of the sponsor or when a trial to test efficacy begins. The information shall consist of eligibility criteria, location of trial sites, point of contact, in a form readily understood by the public, and must be forwarded to the data bank by the sponsor of the trail not later than 21 days after the approval by the FDA; (B) information pertaining to treatments that may be available under a treatment investigational new drug application that has been submitted to the FDA under pertinent regulations or as a Group C cancer drug. The Bank may include information relating to the results of clinical trials, with the consent of the sponsor, including potential toxicities or adverse effects. It shall not include information relating to an investigation if the sponsor has certified to the Secretary that disclosure will substantially interfere with the timely enrollment of subjects in the investigation. To carry out the program, the bill authorizes to be appropriated such sums as may be necessary, and fees collected under section 736 of the Act shall not be used or appropriated for this.

Section 808(b) provides that the Secretary, the Director of NIH, and the Commissioner shall collaborate to determine the feasibility of including device investigations within the registry. Within two years of enactment, the Secretary must prepare and submit to the Senate Committee on Labor and Human Resources and the House Committee on Commerce a report that considers, among other things, the public health need for including devices and the adverse impact, if any, on device innovation and research if information on devices is publicly disclosed.

Sec. 809. Application of Federal Law to the Practice of Pharmacy Compounding.

Section 809 amends section 503 of the FFDCA by adding the new subsection (h). New subsection (h)(1) provides that sections 501(a)(2)(B) [Adulterated drug], 502(f)(1) [Misbranded drug], 502(1) [Antibiotic drug], 505 [New drugs], and 507 [Certification of antibiotics] shall not apply to a drug product that is compounded for an identified patient based on a medical need for a compounded product (1) by a licensed pharmacist in a State licensed pharmacy or Federal facility or licensed physician on the prescription order of a physician or other licensed practitioner authorized by State law to prescribe drugs; (2) by a licensed pharmacist or licensed physician in limited quantities, before receiving a valid prescription order for an identified individual if the compounding of the drug is based on a history of receiving valid orders that have been generated solely within an established relationship between the phar-

macist and the individual patient or the physician or other licensed practitioner who will write the prescription order.

The above noted sections of the FFDCE shall not apply to a drug product if the pharmacist or physician (1) compounds a drug product using bulk drug substances that meet the requirements of this section; (2) compounds a drug product using ingredients other than bulk drug substances that comply with an applicable U.S. Pharmacopeia monograph and the U.S. Pharmacopeia chapter on pharmacy compounding; (3) does no more than advertise or promote the compounding service and does not advertise or promote the compounding of a particular drug, class of drug or type of drug; (4) does not compound a drug product that appears on a list published by the Secretary of drug products that have been withdrawn or removed from market because it is unsafe or not effective; (5) does not compound a particular drug product that is identified by the Secretary in regulation as having demonstrable difficulties in being compounded that reasonably demonstrate an adverse affect on the safety and effectiveness of that drug product; and (6) does not distribute compounded drugs outside the State in which the pharmacy is located, unless the State agency of jurisdiction has entered into a memorandum of understanding (MOU) with the Secretary based on adequate regulation of compounding performed in the State, which provides for appropriate investigation of complaints by the State agency relating to compounded products distributed outside the State.

In cooperation with the National Association of Boards of Pharmacy, the Secretary is required to develop a standard MOU for use by States in complying with the subsection relating to distribution outside the State. Until 180 days after the standard MOU is developed or the date entered in the MOU, whichever is first, the subsection relating to distribution outside the State [new section 503(h)(2)(vi)] does not apply to a pharmacist or physician who does not distribute inordinate amounts of compounded drugs out of State.

Section 809(b) requires the Secretary, after consultation with the U.S. Pharmacopeia, to develop regulations limiting compounding to drug substances that are components of drug products approved by the Secretary and other substances identified by the Secretary. Sections 809 (c) and (d) state that new section 503(h)(1) shall not apply to compounded positron emission tomography drugs, as defined in section 202(jj), or radiopharmaceuticals.

VIII. ADDITIONAL VIEWS

ADDITIONAL VIEWS OF SENATORS GREGG AND MCCONNELL

During the course of the Committee's consideration of S. 830, Senator Gregg offered, and subsequently withdrew, an amendment to modify the PDUFA "maintenance of effort" requirement as proposed for authorization by this legislation. This amendment would have created critical protections for the FDA budget while instituting a realistic budgetary foundation for the PDUFA reauthorization provisions contained in S. 830.

The goal of the amendment was to ensure that the FDA budget may not take a reduction in the Agency's base appropriation level at a percentage greater than the percentage by which the 602(b) allocation of the Agriculture Subcommittee of Appropriations was reduced in order for the "trigger"—FDA's ability to collect and spend industry-paid user fees—to be activated. The mutual agreement of the FDA and the pharmaceutical industry holds promising benefits for the health and welfare of American patients. We are concerned, however, that the absence of thorough discussions on the relationship between the reauthorization of PDUFA and Congress' efforts to attain a balanced budget may undermine these objectives.

During the course of the Committee consideration, the Members of the Committee were never provided with information to clarify the level of total agency appropriations necessary in each of the next five fiscal years to "trigger" the collection of user fees for new human drugs. According to the FDA, in written response to questions asked by Members of the Senate, the base year funding required in FY 1997—the last year of the current PDUFA program—the FDA must dedicate $125.794 million in appropriated funds to human prescription drugs reviews. In FY 1998, under current law requirements, the FDA would have to dedicate over $128.833 million to these activities. However, it is apparent that the FDA does not even have a clearly defined system of checks and balances agency-wide; while they are able to produce accounting reports associated with PDUFA, they are unable to provide Congress with reports of equivalent quality for the total agency appropriation. In addition, it is unclear as to whether the FDA is dedicating a disproportionate amount of funds to these activities at the expense of other accounts, such as those funds that are intended to be expended on the review of medical devices, foods, or generic drugs, which are not covered by user fee agreements.

Further, the Administration requested 8% reduction, $68 million, for the FDA's FY 1998 appropriations. To "replace" these funds, the OMB assumed $131 million in unauthorized user fees with no indi-

cation of the likelihood for industry or Congressional approval and little information on the validity of OMB's assumption regarding these requested funds. This, coupled with the assumption that FDA will not see any changes in its mandated mission—for example, a transfer of a regulatory and fiscal obligation such as ensuring seafood safety from FDA to USDA—puts Congress in the uncomfortable position of trying to maintain funding for activities that may or may not remain relevant during the five year period of this reauthorization.

Clearly, PDUFA's continued role as a source of supplemental, not replacement, fund is important to the prescription drug industry and the consumers it serves. We feel that the direction of this amendment provides a reasonable middle ground between the mutual objectives of industry and the FDA and the Administration's balanced budget mode. This amendment recognizes the importance of the FDA as a national public health agency and that it should not be a site for "found money" within the Agricultural account, while it acknowledges that 602(b) allocations conceivably may experience reduction in future years.

We believe that the Secretary of Health and Human Services sent the Committee a clear signal of concurrence in a letter addressed to the Chairman, dated June 11, 1997, when she wrote:

> We would support a user fee proposal that is consistent with our FY 1998 Budget proposal, but we are concerned that the proposal to collect user fees in this legislation imposes additional pressure on the fixed level of discretionary resources agreed to under the Bipartisan Budget Agreement.

While we believe that cooperative discussions with the Appropriations Committee and the Administration can best address this issue, it is of utmost importance that the Members of this Committee recognize the seriousness of this matter to PDUFA's future. We are confident that this Committee does not intend to reauthorize PDUFA in a manner that could potentially prohibit the Agency's ability to collect the agreed upon fees, nor to force the Appropriations Committee to act independently of the reauthorization provisions in order to make PDUFA work.

We hope that the broader involvement of Members of the Appropriations Committee and the Administration will provide the fiscal framework necessary to the successful resolution of this important matter for American patients and pharmaceutical providers.

JUDD GREGG.
MITCH MCCONNELL.

ADDITIONAL VIEWS OF SENATOR HARKIN

While I strongly support meaningful reform of the Food Drug and Cosmetics Act, I voted against S. 830 because I believe that critical improvements must be made to the provision relating to accredited review of medical devices. In addition, I do not believe the bill goes far enough to improve the post-market surveillance of high risk, potentially life-threatening devices.

The provision relating to accredited party review is described as a "pilot" to test whether the use of third party reviewers would reduce delays in medical device approvals. But the provision is overly broad in scope and it is my hope that the "pilot" can be altered to address the concerns outlined below.

The "pilot" in S. 830 does not limit in any way the number and types of products that may go through a third party reviewer. I believe a test of third party review should be limited to less complex devices that pose a smaller potential risk to patients should this new review process prove ineffective. This is simply common sense. If we plan to test an unproven process, let's do so in a manner that regardless of outcome, poses the least amount of risk to public health and safety.

There are provisions in S. 830 giving FDA final product review authority, but I am concerned that a 30 or 60 day time limit for FDA action will be extremely difficult, or impossible, for the Agency to meet.

In addition, under S. 830 the manufacturer of the device selects the reviewer and also directly pays the reviewer. Direct payment by the manufacturer of the reviewer, without approval or even review by FDA, creates obvious conflicts of interest. Under FDA's current third party review regulations, the Agency has the authority to review compensation agreements between the manufacturer and the reviewer. However, the bill does not provide FDA full and clear authority in this area. I believe the FDA should have the authority in the statue to review payment agreements and check for conflict of interest.

I am also concerned that this bill fails to provide adequate performance criteria for the post market surveillance of sophisticated, potentially life-threatening medical devices. If this bill requires the Agency to be more efficient during the approval process, I believe we need to make extra sure the FDA strengthens its efforts to track and monitor products that would present a danger to the public health should they be found to be unsafe or ineffective.

TOM HARKIN.

ADDITIONAL VIEWS OF SENATOR MURRAY

I strongly endorse FDA modernization and reform which is why I voted to report S. 830 out of committee. But, I believe that several points need to be made to clarify my position on this legislation. First, I would like to make a few comments on the process and express my concerns regarding this pending bill. First, I do want to recognize the work that you and your staff have done in developing this measure. I appreciate your efforts to work to correct some of my concerns and your willingness to craft acceptable language when appropriate.

Having said that, I do need to express some concerns with this process. As a new member of this committee I did not have the benefit of being here for last year's mark-up where many of these issues were discussed and debated at length. I realize that we did have two hearings on FDA reform, but one primarily focused on PDUFA. As we all know, these issues are far from simple and in most cases are extremely complicated. In addition, the implications of what we do or don't do are significant.

There has been limited time to review your draft and the many amendments under consideration. In light of the important public health issues involved I believe that the prudent course would have been to schedule a hearing on your draft in order to hear testimony from expert witnesses as to the ramifications of each section.

My objective all along has been to reform FDA, to revitalize a public health agency that faces life or death decisions every day. One of the reasons I worked to secure a position on this committee is because I wanted to play a direct role in health care policy—FDA is one of the most critical health care policy issues this committee will consider in the 105th Congress. We have an opportunity to improve access to health care products for million of Americans. Effective reform of the FDA can be a life saver.

I do want to make it clear that there are some real reform proposals included in the bill that will serve to improve the overall performance of the FDA. I want to thank the Chairman for including some of these items.

I am here today because I made the decision several years ago, to be an advocate for children. I got directly involved in the political process because I was concerned that the voices of children were not being heard. I have always considered children's issues my top priorities. Because of this, I am pleased that included in the legislation is the Dodd/Dewine Pediatric Studies Marketing Exclusivity title. I believe that the FDA has not done enough to encourage greater pediatric clinical trials. For too long children have simply been ignored. Providing patent exclusivity incentives to companies to include children in clinical trails may be the push that the industry needs. I realize that there are some questions and concerns about this approach, but unfortunately, this is the only solu-

tion I have seen that will work. I am hopeful that we can address some of the concerns of the generic drug manufacturers. No one wants to increase the cost of health care, but if children are denied life saving treatments or are unable to benefit from break through drugs that can reduce the severity of their illness, we have saved in the long run. I am willing to work on some type of transitional language or criteria for the Secretary's selection process, but honestly believe we have an obligation to expand clinical trial to include children.

I would also like to point out that the improvements made in the expansion of the humanitarian use of devices will provide life saving alternatives to physicians and patients.

I am also pleased that the Chairman has worked to improve collaboration and communication between the FDA and industry. The language in the bill does require more collaboration between the FDA and industry throughout the approval process, but this should be seen as a positive step, not a burden on the agency. Success is much easier to obtain if the FDA and the industry work more as a team with clear expectations and open lines of communications.

It is unfortunate that due to many of the more controversial issues, we have not talked much about Title VII—PDUFA reauthorization. This is one of the most positive aspects of the bill and illustrates the success we can achieve when we all share the same objectives and priorities. Title VII establishes new performance standards for the FDA that will only improve the process. I want to commend the FDA for putting forth this reauthorization language and working with, not against industry and the patients.

Despite the many positive improvements, the current draft of the pending legislation has some serious flaws and I am concerned that in an effort to reform and revitalize the FDA, we weaken their role as a public health agency. Despite modifications, I am still concerned about some of the proposed changes on substantial evidenc—we simply cannot and should not act to limit the ability of the FDA to require comprehensive clinical trials. I believe that the current Guidance Document that governs FDA practices does offer each investigator the "guidance" necessary to determine the number of clinical trails necessary—I am still not convinced that the proposal before use today will actually clarify, but rather limit the ability of FDA to require two trials in order to replicate science.

One of the most significant problems facing FDA is the approval, tracking and surveillance of medical devices. Because of a lack of targeted resources, the FDA has been unable to ensure timely approval for many, life saving devices. I would acknowledge that the agency has made some improvements in this process, but I still believe that we need some reform and innovative solutions. There are several proposed solutions to the device approval delays. One approach that I do believe has some merit is a third party review process. But, if the objective to by-pass the FDA, privitize the FDA, as opposed to enhancing the activities of the FDA, than I would recommend we seek other solutions. From the language in the Chairman's current bill, it appears that the structure of the third party review, the types of devices that could be approved by a third party and the inherent conflict of interest questions could jeopardize the public health. I have still not seen any assurance that the

public's health and safety would not be jeopardized and that the current language would truly enhance the FDA's role as the lead agency for device approval. I am still not convinced that adding another layer of "bureaucracy" will improve the approval process—beyond the improvements already achieved by FDA. I have several other concerns regarding the device tracking and surveillance provisions in the bill and am some what disappointed that so much controversy has surrounded one of the most pressing FDA reform issues—that is improving and streamlining the device approval, surveillance and tracking processes.

I also believe it is essential that the Gregg amendment which preempts a State's ability to enact labeling restriction or requirements on over the counter drugs needs to be revised. This amendment could effectively prohibit a State from requiring warning labels on harmful medications unless they first petitioned the FDA for this ability. A State should not have to petition FDA in order to require warning labels, such as Mr. Yuk, which is an important tool in protecting children. While Mr. Yuk may be a voluntary, education campaign, States should have the ability to require this kind of labeling. Seeking FDA approval is clearly an unfunded mandate on the States. While uniformity may be the objective of the Gregg amendment, I am concerned that the unintended consequence could be harmful for children.

There are several other areas that I believe need greater clarification and do not want to delay this process any further, except to say that I am concerned that many of these provisions could jeopardize FDA reform and revitalization efforts. In addition, the timely reauthorization of PDUFA is threatened by much of what we do here today. This in itself deeply troubles me.

I am planning on voting to report this measure out of the committee because of the urgency in moving this legislation to the floor. I do so with some hesitation, but I sincerely believe that moving this process along is a positive step and essential for meeting my goal of a public debate on the issues. However, the current bill still has many flaws that must be adequately addressed before this bill can be sent to the President. I am hopeful that I can continue to work with the Chairman to improve the legislation without threatening the many positive provisions. Without substantial changes and revisions I would have a difficult time supporting this legislation on the floor. I hope that we can all work to achieve real reform that improves the regulatory process, but does not weaken an agency that many of us simply take for granted. What may have been lost in all of this is the fact that the FDA's number one priority is and should always be, guarding the public's health and safety.

Thank you, Mr. Chairman.

PATTY MURRAY.

IX. MINORITY VIEWS OF SENATORS KENNEDY, BINGAMAN, AND REED

As stated in S. 830 the mission of the Food and Drug Administration is to protect public health including ensuring that drugs and devices are safe and effective and that food is wholesome. S. 830 presents a sweeping package of changes that will impact every family that fills a prescription, depends upon a medical device, or relies on food labels to choose the healthiest products for their dinner table.

Many of the provisions included in this bill are consensus items with broad, bipartisan support. If we were to report legislation today that includes *only* the items on which consensus has been achieved, we would have crafted the broadest FDA reform legislation in decades—reforms that could pass the Senate unanimously.

Unfortunately, despite the progress that has been made, this legislation also includes controversial provisions that threaten public health. These provisions do not improve the FDA—they weaken it. Given these concerns, we oppose the bill as currently drafted. If controversial provisions are not modified or eliminated from the bill, it will be difficult to achieve timely reauthorization of the Prescription Drug User Fee Act. We believe Senator Jeffords is committed to trying to work out a consensus on these issues before the legislation goes to the floor—and we are committed to working with him.

PRESCRIPTION DRUG USER FEE ACT (PDUFA) REAUTHORIZATION

The most important of the consensus items in this bill is the reauthorization of the Prescription Drug User Fee Act. This committee authored the Prescription Drug User Fee Act in 1992. This legislation is one of the most effective regulatory reform programs ever enacted. The bill established a new partnership between the industry and the agency. The industry agreed to provide additional, resources; the agency agreed to measurable performance standards to speed the review of products. Every goal set by that legislation for the FDA has not only been met, it has been exceeded.

Today, the FDA is unequalled in the world in its record of getting new drugs quickly to market without sacrificing patient protection. In fact, last year, average review times in the United States were twice as fast as in Europe. Fifteen new drugs were approved in both the European Union and the United States—and in 80 percent of the cases, the United States approved the new drugs either first or at the same time as the European Union. More companies chose the United States for the introduction of breakthrough drugs than any other country.

The Prescription Drug User Fee Act reauthorization, as negotiated between the FDA and industry and contained in this bill, will maintain and enhance the progress that has been achieved.

Especially important is the promotion of early cooperation between the FDA and industry in order to reduce total drug development time, not just FDA review time. This legislation is vital, and speedy action is essential. If this legislation is not passed by August 1, the FDA will have to begin sending lay-off notices to the 600 employees who are supported through user fees and who are vital to the timely review of drugs and biologics. We are committed to ensuring the timely passage of PDUFA in combination with consensus reforms.

DRUG PROVISIONS

Other important consensus provisions in this bill clarify that FDA may approve drugs and biologics on the basis of products manufactured in pilot and small scale facilities; direct FDA to propose regulations governing the approval of diagnostic and monitoring radiopharmaceuticals; codify agency policies regarding modernization of biologics approvals; establish a mechanism for the FDA to review manufacturing changes for drugs; require the Agency to issue guidance streamlining data submissions for drugs and biologics; and provide incentives to encourage drug manufacturers to conduct studies on pediatric uses of specified drugs. The bill also establishes a "fast track" mechanism to facilitate the development and expedited approval of new drugs intended for the treatment of serious and life-threatening conditions.

These provisions address a number of industry concerns and improve the predictability and efficiency of drug approval and manufacturing. In recent years, in partnership with Congress and the Administration, the FDA has responded to criticism and alleged delays in approving new products by taking impressive steps to improve its performance. Provisions in this bill will codify some of the important practices that the FDA has established to reduce unnecessary regulatory burdens on industry and to modernize its regulatory processes. These steps have added up to a quiet revolution in the way the FDA fulfills its critical missions.

CONCERNS RELATED TO DRUGS AND BIOLOGICS

Included in this bill is a provision to allow distribution of health economic claims to formularly committees and managed care organizations. Health economics is a developing area with standards and guidelines that even the experts do not agree upon. While this is an important area that should eventually be addressed, there has not been time to adequately reflect on the complex questions presented. The language included in the bill has not been considered in public hearings nor have patient groups had an opportunity to provide input on this issue.

The FDA is developing a policy on regulation of pharmacoeconomic data which deals with the fundamental questions related to data to support claims of cost-effectiveness. These fundamental questions should be dealt with before enactment of any statutory changes. A more reasonable provision would require the agency to develop a policy on regulation of pharmacoeconomics. Such a policy would lay the groundwork for consideration of distribution of pharmacoeconomic claims to formularies and managed care organizations. Without this groundwork, there is a danger that policies related to dissemination of health economic informa-

tion will become an avenue for off-label promotion of unsubstantiated clinical efficacy claims. It is not clear why a controversial provision related to health economics that has not had adequate public consideration should be attached to this bill.

Issues not included in the current bill must also be addressed before a balanced reform package for drugs and biologics can be achieved. This is particularly important in the area of enforcement. The citizens of this country expect the FDA to protect them from unsafe or ineffective drugs and biologics. We must provide FDA with the tools needed to carry out this mission.

This is particularly important under circumstances where FDA has been given the authority to approve drugs and biologics in an accelerated mode. In the early 1990's, new regulations made it possible for the FDA to grant marketing approval under accelerated reviews to drugs used to treat serious and life-threatening illnesses. Under these programs, and under the proposed fast track program, surrogate endpoints may be used to provide early indications of potential clinical benefit. While these endpoints are useful for getting drugs to patients faster, it is essential that adequate phase IV, post-marketing studies be performed to determine the ultimate safety and efficacy of the drug.

A 1996 report by the Department of Health and Human Services Inspector General on postmarketing studies of new molecular entities indicated that 77 percent of phase IV studies requested between 1987 and 1993 were in progress or have been submitted to the agency. Of the 23 percent that were not in progress or submitted, approximately 6 percent of these studies will not be conducted because the FDA released the company from their commitment. Of the remaining studies that were not in progress or submitted, 11 percent or over 40 studies had not been completed for reasons that were unknown or because the company had simply failed to fulfill its responsibility. In some of these cases, over 6 years have elapsed and the companies still insist that their studies will begin sometime in the future.

The FDA should have the authority to enforce a request for postmarket or confirmatory clinical trials especially when this data is pursuant to an accelerated approval of a new drug. If a company fails to complete a requested trial, currently the only remedy available to the Secretary is to remove the drug from the market. Even if the process of withdrawal is expedited, this remains a cumbersome process which punishes patients who depend upon the drug in question. The Patient Coalition regards enforcement procedures for phase IV studies as a high priority. If we are truly trying to enhance patient access to important medicines by providing accelerated approvals, we should be prepared to assure that these drugs are truly safe and effective.

The FDA should be given the authority to impose intermediate sanctions of civil money penalties for failure to perform post-approval research. When phase IV studies are needed, they provide critically important data to assure safety and effectiveness of new drugs. Failure to enforce these requirements is unfair to those companies who do fulfill their obligations. We must devise fair procedures that will assure that all companies complete required studies in a timely manner.

DEVICE PROVISIONS

We have worked hard to balance the need for changes to device approval processes with protection of public health. Although a number of consensus device reform provisions have been agreed upon, we are concerned that, on balance, this bill weakens patient protections from unsafe medical devices. It is important to note that the Safe Medical Devices Act of 1990 was enacted because medical device oversight in this country was deemed inadequate and placed patients at risk. It is also important to note that the FDA has made significant improvements in the area of device approval.

Even without additional resources in the device area, the FDA's recent achievements have been impressive. So-called 510(k) applications—devices which are reviewed by the FDA to determine their substantial equivalence to a device already on the market—account for 98 percent of all device submissions. The FDA has now essentially eliminated its backlog. Last year, it reviewed 94 percent of these devices within the statutory time frame—compared to only 40 percent just 4 years ago.

In the area of Class III devices, where most problems remain, the FDA has improved its performance substantially. According to a study by the General Accounting Office, median review times dropped 60 percent between 1991 and 1996. A recent survey of device industry executives reported that the business climate for the industry is the best in the 5 year history of the survey. The sponsor of the survey attributes this favorable response, in large measure, to improvements at FDA, and concludes, "The agency has not only reduced the produce approval delays that slowed new product introductions, but, perhaps more importantly, has also greatly reduced both executives' and investors' uncertainty about the timeliness of future product introductions."

We support many of the device reform provisions included in the bill. We agree that FDA should be granted the authority to recognize performance standards established by nationally or internationally recognized standard setting entities. We encourage implementation of a system that will provide for appropriate industry and public input concerning which standards should be accepted.

We also support provisions that would require FDA to exempt certain class devices from premarket notification requirements; allow use of data from a premarket approval 6 years after approval of the first device of a type; require the FDA to issue a regulation establishing criteria to be used in determining when a specific intended use of a device is not included in a general use; and provide mechanisms for preventing inappropriate classification of low or moderate risk devices into Class III.

CONCERNS RELATED TO DEVICES

We remain very concerned with provisions in the bill that turn over reviews of critical medical devices to private companies selected and paid by the very industry they are supposed to regulate. The FDA currently has a pilot project to explore this concept with low risk devices. Some expansion of this pilot is warranted. But to test this concept by turning over the regulation of the most sen-

sitive and potentially dangerous devices to private companies chosen and paid by the manufacturer is an unacceptable experiment with the public's health. No manufacturer will choose a reviewing company that it thinks is going to be too rigorous. Every reviewing company knows that its prospects for future business—and even the generosity of its fees—are likely to depend on decisions that are favorable to the manufacturer.

Americans today have a high degree of protection against unsafe and ineffective devices, because these devices have been reviewed by the professional, capable, objective public officials at the FDA, who owe allegiance to no interest except the public interest.

The American people deserve protection from unsafe heart valves and pacemakers, inaccurate imaging machines used to detect breast cancer or brain tumors, faulty drug infusion pumps, and other unsafe and ineffective medical technologies. They should not have to rely for that protection on untested private companies hired and paid by the very firms producing the potentially faulty products.

In addition the bill also allows device manufacturers to manipulate the product label to avoid careful FDA scrutiny and to make basic changes in the manufacturing process without effective FDA oversight, even if those changes threaten the sterility, the safety, or the effectiveness of the product. The bill establishes a mechanism for automatic reclassification of class III devices without a clear standard for subsequent review of the product. Post-market surveillance is arbitrarily limited to an initial 24-month period even on products where longer surveillance will clearly be required. The cumulative effect of these and several other provisions, is to weaken the FDA's ability to assure safety and effectiveness of medical devices.

FOOD PROVISIONS

We support the inclusion of a consensus provision on food contact substances that has been endorsed by both the FDA and the food industry.

We cannot support the inclusion of a provision that would weaken the FDA's oversight of food health claims. The Nutrition Labelling and Education Act of 1990 established landmark requirements for food labelling that give consumers the right to the information they need in order to choose healthy products for the family dinner table. This legislation would undermine that important right by allowing manufacturers to make health claims that could be misleading and even inaccurate. This faulty provision in the bill is strongly opposed by 20 leading health and consumer organizations, including the American Cancer Society, the American Heart Association, the National Council on the Aging, and the Consumer Federation of America.

Weakening FDA oversight of health claims would allow food companies to use scientific statements about nutrition and health made by other government agencies as a basis for health claims—even if such statements are not supported by "significant scientific agreement". For example, in 1980 the Food and Nutrition Board, an arm of the National Academy of Sciences, published a report stating that Americans need not cut back on cholesterol in order to reduce

their risk of heart disease. The report's findings were disputed by the American Medical Association, the American Heart Association, and many other public health and medical organizations. This and other cases underscore the need to assign the job of pre-clearing health claims to a single regulatory agency that can sort through the data and determine if a claim is supported by "significant scientific agreement".

CUMULATIVE AGENCY BURDENS WITHOUT NEW RESOURCES

At a time when agency resources are scarce and demands for rapid product review are increasing, this bill will impose a number of new bureaucratic burdens. Eighteen new statutory deadlines are mandated and twenty Federal Register documents must be produced, including 12 regulations by February 1999. Excluding new statutory deadlines and required Federal Register documents, an additional 28 new statutory tasks will be required. A disproportionate share of new bureaucratic requirements fall on the Center for Devices and Radiological Health (CDRH).

There are few more important agencies of the federal government than the Food an Drug Administration. The FDA is responsible for assuring the Nation's food supply is pure and health. The FDA provides a guarantee that the drugs and devices we rely on to cure or treat diseases are safe and effective. If it does its job well, the FDA can speed medical miracles from the laboratory bench to the patient's bedside. If the agency does its job poorly, it can expose millions of Americans to unsafe or ineffective medical products and jeopardize the safety of our food.

Given the importance of the FDA to the American public, any reform of this agency should have the broadcast bipartisan support. We must work together to reach agreement on provisions in this bill that will allow the FDA to do its job well and build on the successes of the Prescription Drug User Fee Act.

EDWARD M. KENNEDY.
JEFF BINGAMAN.
JACK REED.

X. CHANGES IN EXISTING LAW

In compliance with rule XXVI paragraph 12 of the Standing Rules of the Senate, the following provides a print of the statute or the part or section thereof to be amended or replaced (existing law proposed to be omitted is enclosed in black brackets, new matter is printed in italic, existing law in which no change is proposed is shown in roman):

FEDERAL FOOD, DRUG, AND COSMETIC ACT

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CHAPTER II—DEFINITIONS

SEC. 201. [321] for the purposes of this Act—(a)(1) * * *

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(hh) * * *

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(ii) In any provision relating to a review of any application or submission (including a petition, notification, and any other similar form of request), made under this Act with respect to an article that is a new drug, device, biological product, new animal drug, and animal feed bearing or containing a new animal drug, color additive, or food additive, that is submitted to the Secretary to obtain marketing approval, to obtain classification of a device under section 513(f)(1), or to establish or clarify the regulatory status of the article—

(1) the term "day" means a calendar day in which the Secretary has responsibility to review such an application or submission; and

(2) a reference to a date relating to receipt of such an application or submission by the Secretary shall be deemed to be a reference to the date on which the Secretary receives a complete application or submission within the meaning of this Act and the regulations promulgated under this Act.

(jj) The term "compounded position emission tomography drug" means a drug that—

(1) exhibits spontaneous disintegration of unstable nuclei, including the emission of positrons;

(2) includes any nonradioactive reagent, reagent kit, ingredient, nuclide generator, accelerator, target material, electronic synthesizer, or other apparatus or computer program to be used in the preparation of any such drug; and

(3)(A) has been compounded in a State in accordance with State law for a patient or for research, teaching, or quality control by or on the order of a practitioner licensed by that State to compound or order such a drug; or

(B) has been compounded in a Federal facility in a State in accordance with the law of the State in which the facility is located.

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CHAPTER III—PROHIBITED ACTS AND PENALTIES

PROHIBITED ACTS

SEC. 301. * * *

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SEIZURE

SEC. 304. [334] (a)(1) * * *

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(d)(1) Any food, drug, device, or cosmetic condemned under this section shall, after entry of the decree, be disposed of by destruction or sale as the court may, in accordance with the provisions of this section, direct and the proceeds thereof, if sold, less the legal costs and charges, shall be paid into the Treasury of the United States; but such article shall not be sold under such decree contrary to the provisions of this Act or the laws of the jurisdiction in which sold. After entry of the decree and upon the payment of the costs of such proceedings and the execution of a good and sufficient bond conditioned that such article shall not be sold or disposed of contrary to the provisions of this Act or the laws of any State or Territory in which sold, the court may by order direct that such article be delivered to the owner thereof to be destroyed or brought into compliance with the provisions of this Act under the supervision of an officer or employee duly designated by the Secretary, and the expenses of such supervision shall be paid by the person obtaining release of the article under bond. If the article was imported into the United States and the person seeking its release establishes (A) that the adulteration, misbranding, or violation did not occur after the article was imported, and (B) that he had no cause for believing that it was adulterated, misbranded, or in violation before it was released from customs custody, the court may permit the article to be delivered to the owner for exportation in lieu of destruction upon a showing by the owner that all of the conditions of section 801(e) can and will be met. The provisions of this sentence shall not apply where condemnation is based upon violation of section 402(a) (1), (2), or (6), section 501(a)(3), section 502(j), or section 601 (a) or (d). Where such exportation is made to the original foreign supplier, then [paragraphs (1) and (2) of section 801(e)] subparagraphs (A) and (B) of section 801(e)(1) and the preceding sentence shall not be applicable; and in all cases of exportation the bond shall be conditioned that the article shall not be sold or disposed of until the applicable conditions of section 801(e) have been met. *Any person seeking to export an imported article pursuant to any of the provisions of this subsection shall establish that the article was intended for export at the time the article entered commerce.* Any article condemned by reason of its being an

article which may not, under section 404 or 505, be introduced into interstate commerce, shall be disposed of by destruction.

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(l) The using, on the labeling of any drug or device or in any advertising relating to such drug or device, of any representation or suggestion that approval of an application with respect to such drug or device is in effect under section 505, 515, or 520(g), as the case may be, or that such drug or device complies with the provisions of such section.

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(w) * * *

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(x) The falsification of a declaration of conformity submitted under subsection (c) of section 514 or the failure or refusal to provide data or information requested by the Secretary under section 514(c)(3).

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MISBRANDED FOOD

SEC. 403. * * *

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(r)(1) * * *

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(3)(A) * * *

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(C) Notwithstanding the provisions of clauses (A)(i) and (B), a claim of the type described in subparagraph (1)(B) that is not authorized by the Secretary in a regulation promulgated in accordance with clause (B) shall be authorized and may be made if—

(i) an authoritative scientific body of the Federal Government with official responsibility for public health protection or research directly relating to human nutrition (such as the National Institutes of Health or the Centers for Disease Control and Prevention), the National Academy of Sciences, or a subdivision of the scientific body or the National Academy of Sciences, has published an authoritative statement, which is currently in effect, about the relationship between a nutrient and a disease or health-related condition to which the claim refers;

(ii) a person has submitted to the Secretary at least 90 days before the first introduction of a food into interstate commerce a notice of the claim, including a concise description of the basis upon which such person relied for determining that the requirements of subclause (i) have been satisfied;

(iii) the claim and the food for which the claim is made are in compliance with clause (A)(ii), and are otherwise in compliance with paragraph (a) and section 201(n); and

(iv) the claim is stated in a manner so that the claim is an accurate representation of the authoritative statement referred to in subclause (i) and so that the claim enables the public to

comprehend the information provided in the claim and to understand the relative significance of such information in the context of a total daily diet.

For purposes of this paragraph, a statement shall be regarded as an authoritative statement of such a scientific body described in subclause (i) only if the statement is published by the scientific body and shall not include a statement of an employee of the scientific body made in the individual capacity of the employee.

(D) A claim meeting the requirements of clause (C) may be made until—

(i) such time as the Secretary issues a final regulation under clause (B) prohibiting or modifying the claim, and the regulations has become effective; or

(ii) a district court of the United States in an enforcement proceeding under chapter III has determined that the requirements of clause (C) have not been met.

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FOOD ADDITIVES

Unsafe Food Additives

SEC. 409. (a) A food additive shall, with respect to any particular use or intended use of such additives, be deemed to be unsafe for the purposes of the application of clause (2)(C) of section 402(a), unless—

(1) it and its use or intended use conform to the terms of an exemption which is in effect pursuant to [subsection (i)] of this section; [or]

(2) there is in effect, and it and its use or intended use are in conformity with, a regulation issued under this section prescribing the conditions under which such additive may be safely used[.]*; or*

(3) in the case of a food additive as defined in this Act that is a food contact substance, there is—

(A) in effect, and such substance and the use of such substance are in conformity with, a regulation issued under this section prescribing the conditions under which such additive may be safely used; or

(B) a notification submitted under subsection (h) that is effective.

[While such a regulation relating to a food additive is in effect, a food shall not, reason of bearing or containing such an additive in accordance with the regulation, be considered adulterated within the meaning of clause (1) of section 402(a).]

While such a regulation relating to a food additive, or such a notification under subsection (h) relating to a food additive that is a food contact substance, is in effect, and has not been revoked pursuant to subsection (i), a food shall not, by reason of bearing or containing such a food additive in accordance with the regulation or notification, be considered adulterated under section 402(a)(1).

Notification Relating to a Food Contact Substance

(h)(1) Subject to such regulations as may be promulgated under paragraph (3), a manufacturer or supplier of a food contact substance may, at least 120 days prior to the introduction or delivery for introduction into interstate commerce of the food contact substance, notify the Secretary of the identity and intended use of the food contact substance, and of the determination of the manufacturer or supplier that the intended use of such food contact substance is safe under the standard described in subsection (c)(3)(A). The notification shall contain the information that forms the basis of the determination, the fee required under paragraph (5), and all information required to be submitted by regulations promulgated by the Secretary.

(2)(A) A notification submitted under paragraph (1) shall become effective 120 days after the date of receipt by the Secretary and the food contact substance may be introduced or delivered for introduction into interstate commerce, unless the Secretary makes a determination within the 120-day period that, based on the data and information before the Secretary, such use of the food contact substance has not been shown to be safe under the standard described in subsection (c)(3)(A), and informs the manufacturer or supplier of such determination.

(B) A decision by the Secretary to object to a notification shall constitute final agency action subject to judicial review.

(C) In this paragraph, the term "food contact substance" means the substance that is the subject of a notification submitted under paragraph (1), and does not include a similar or identical substance manufactured or prepared by a person other than the manufacturer identified in the notification.

(3)(A) The process in this subsection shall be utilized for authorizing the marketing of a food contact substance except where the Secretary determines that submission and review of a petition under subsection (b) is necessary to provide adequate assurance of safety, or where the Secretary and any manufacturer or supplier agree that such manufacturer or supplier may submit a petition under subsection (b).

(B) The Secretary is authorized to promulgate regulations to identify the circumstances in which a petition shall be filed under subsection (b), and shall consider criteria such as the probable consumption of such food contact substance and potential toxicity of the food contact substance in determining the circumstances in which a petition shall be filed under subsection (b).

(4) The Secretary shall keep confidential any information provided in a notification under paragraph (1) for 120 days after receipt by the Secretary of the notification. After the expiration of such 120 days, the information shall be available to any interested party except for any matter in the notification that is a trade secret or confidential commercial information.

(5)(A) Each person that submits a notification regarding a food contact substance under this section shall be subject to the payment of a reasonable fee. The fee shall be based on the resources required to process the notification including reasonable administrative costs for such processing.

(B) The Secretary shall conduct a study of the costs of administering the notification program established under this section and, on the basis of the results of such study, shall, within 18 months after the date of enactment of the Food ad Drug Administration Modernization and Accountability Act of 1997, promulgate regulations establishing the fee required by subparagraph (A).

(C) A notification submitted without the appropriate fee is not complete and shall not become effective for the purposes of subsection (a)(3) until the appropriate fee is paid.

(D) Fees collected pursuant to this subsection—

(i) shall not be deposited as an offsetting collection to the appropriations for the Department of Health and Human Services;

(ii) shall be credited to the appropriate account of the Food and Drug Administration; and

(iii) shall be available in accordance with appropriation Acts until expended, without fiscal year limitation.

(6) In this section, the term "food contact substance" means any substance intended for use as a component of materials used in manufacturing, packing, packaging, transporting, or holding food if such use is not intended to have any technical effect in such food.

Amendment or Repeal of Regulations

[h**]** *(i)* The Secretary shall by regulation prescribe the procedure by which regulations under the foregoing provisions of this section may be amended or repealed, and such procedure shall conform to the procedure provided in this section for the promulgation of such regulations.

Exemptions for Investigational Use

[i**]** *(j)* Without regard to **[**subsections (b) to (h)**]** *subsections (b) to (i)*, inclusive, of this section, the Secretary shall be regulation provide for exempting from the requirements of this section any food additive, and any food bearing or containing such additive, intended solely for investigational use by qualified experts when in his opinion such exemption is consistent with the public health.

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CHAPTER V—DRUGS AND DEVICES

SUBCHAPTER A—DRUGS AND DEVICES

ADULTERATED DRUGS AND DEVICES

SEC. 501. A drug or device shall be deemed to be adulterated—

(a)(1) If it consists in whole or in part of any filthy, putrid, or decomposed substance; or (2)(A) if it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health; or (B) if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity

characteristics, which it purports or is represented to possess[; or (3)]*; or (C) if it is a compounded positron emission tomography drug and the methods used in, or the facilities and controls used for, its compounding, processing, packing, or holding do not conform to or are not operated or administered in conformity with the positron emission tomography compounding standards and the official monographs of the United States Pharmacopoeia to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess; or (3)* if its container is composed, in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health; or (4) if (A) it bears or contains, for purposes of coloring only, a color additive which is unsafe within the meaning of section 721(a), or (B) it is a color additive the intended use of which in or on drugs or devices is for purposes of coloring only and is unsafe within the meaning of section 721(a); or (5) if it is a new animal drug which is unsafe within the meaning of section 512; or (6) if it is an animal feed bearing or containing a new animal drug, and such animal feed is unsafe within the meaning of section 512.

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[(e)] *(e)(1)* If it is, or purports to be or is represented as, a device which is subject to a performance standard established under section 514, unless such device is in all respects in conformity with such standard.

(2) If it is, declared to be, purports to be, or is represented as, a device that is in conformity with any performance standard recognized under section 514(c) unless such device is in all respects in conformity with such standard.

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MISBRANDED DRUGS AND DEVICES

SEC. 502. * * *

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(u) In the case of a health care economic statement that is included in labeling or advertising provided to formulary committee, managed care organization, or similar entity with responsibility for drug selection decisions (other than the label or approved physician package insert) relating to an indication approved under section 505 or 351 of the Public Health Service Act (42 U.S.C. 262), if the health care economic statement is not based on competent and reliable scientific evidence. The only requirement applicable to any such statement under this Act shall be the requirements of this paragraph. In this paragraph, the term "health care economic statement" means any statement that identifies, measures, or compares the costs (direct, indirect, and intangible) and health care consequences of a drug to another drug, to another health care intervention for the same indication, or to no intervention, where the primary endpoint is an economic outcome.

EXEMPTIONS AND CONSIDERATIONS FOR CERTAIN DRUGS, DEVICES, AND BIOLOGICAL PRODUCTS

SEC 503. * * *

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(b)(1) A drug intended for use by man which—

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[(A) is a habit-forming drug to which section 502(d) applies; or**]**

[(B)**]** *(A)* because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drug; or

[(C)**]** *(B)* is limited by an approved application under section 505 to use under the professional supervision of a practitioner licensed by law to administer such drug;

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(3) The Secretary may by regulation remove drugs subject to **[**section 502(d) and**]** section 505 from the requirements of paragraph (1) of this subsection when such requirements are not necessary for the protection of the public health.

[(4) A drug which is subject to paragraph (1) of this subsection shall be deemed to be misbranded if at any time prior to dispensing its label fails to bear the statement "Caution: Federal law prohibits dispensing without prescription." A drug to which paragraph (1) of this subsection does not apply shall be deemed to be misbranded if at any time prior to dispensing its label bears the caution statement quoted in the preceding sentence.**]**

(4)(A) A drug that is subject to paragraph (1) shall be deemed to be misbranded if at any time prior to dispensing the label of the drug fails to bear, at a minimum, the symbol "Rx only".

(B) A drug to which paragraph (1) does not apply shall be deemed to be misbranded if at any time prior to dispensing the label of the drug bears the symbol described in subparagraph (A).

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(g)(1) * * *

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(4) As used in this subection:

(A) The term "biological product" has the meaning given the term in **[**section 351(a)**]** *section 351(i)* **[**of the Public Health Service Act (42 U.S.C. **[**262(a)**]** *262(i)*).

(B) The term "market clearance" includes—

(i) approval of an application under section 505, 507, 515, or 520(g),

(ii) a finding of substantial equivalence under this subchapter, and

(iii) approval of a **[**product or establishment license under subsection (a) or (d)**]** *biologics license application*

under subsection (a) of section 351 of the Public Health Service Act (42 U.S.C. 262).

* * * * * * *

(h)(1) Sections 502(a)(2)(B), 502(f)(1), 502(l), 505, and 507 shall not apply to a drug product if—

(A) the drug produce is compounded for an identified individual patient based on a medical need for compounded product—

(i) by a licensed pharmacist in a State licensed pharmacy or a Federal facility, or a licensed physician on the prescription order of a licensed physician or other licensed practitioner authorized by State law to prescribe drugs; or

(ii) by a licensed pharmacist or licensed physician in limited quantities, prior to the receipt of a valid prescription order for the identified individual patient, and is compounded based on a history of the licensed pharmacist or licensed physician receiving valid prescription orders for the compounding of the drug product that have been generated solely within an established relationship between the licensed pharmacist, or licensed physician, and—

(I) the individual patient for whom the prescription order will be provided; or

(II) the physician or other licensed practitioner who will write such prescription order; and

(B) the licensed pharmacist or licensed physician—

(i) compounds the drug product using bulk drug substances—

(I) that—

(aa) comply with the standards of an applicable United States Pharmacopeia monograph; or

(bb) in a case in which such a monograph does not exist, or drug substances that are covered by regulations issued by the Secretary under paragraph (3);

(II) that are manufactured by an establishment that is registered under section 510 (including a foreign establishment that is registered under section 510(i)); and

(III) that are accompanied by valid certificates of analysis for each bulk drug substance;

(ii) compounds the drug product using ingredients (other than bulk drug substances) that comply with the standards of an applicable United States Pharmacopeia monograph and the United States Pharmacopeia chapter on pharmacy compounding;

(iii) only advertises or promotes the compounding service provided by the licensed pharmacist or licensed physician and does not advertise or promote the compounding of any particular drug, class of drug, or type of drug;

(iv) does not compound a drug product that appears on a list published by the Secretary in the Federal Register of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective;

(v) does not compound a drug product that is identified by the Secretary in regulation as presenting demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product; and

(vi) does not distribute compounded drugs outside of the State in which the drugs are compounded, unless the principal State agency of jurisdiction that regulates the practice of pharmacy in such State has entered into a memorandum of understanding with the Secretary (based on the adequate regulation of compounding performed in the State) that provides for appropriate investigation by the State agency of complaints relating to compounded products distributed outside of the State.

(2)(A) The Secretary shall, after consultation with the National Association of Boards of Pharmacy, develop a standard memorandum of understanding for use by States in complying with paragraph (1)(B)(vi).

(B) Paragraph (1)(B)(vi) shall not apply to a licensed pharmacist or licensed physician, who does not distribute inordinate amounts of compounded products outside of the State, until—

(i) the date that is 180 days after the development of the standard memorandum of understanding; or

(ii) the date on which the State agency enters into a memorandum of understanding under paragraph (1)(B)(vi), whichever occurs first.

(3) The Secretary, after consultation with the United States pharmacopeia Convention Incorporated, shall promulgate regulations limiting compounding under paragraph (1)(B)(i)(I)(bb) to drug substances that are components of drug products approved by the Secretary and to other drug substances as the Secretary may identify.

(4) The provisions of paragraph (1) shall not apply—

(A) to compounded positron emission tomography drugs as defined in section 202(jj); or

(B) to radiopharmaceuticals.

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NEW DRUGS

SEC. 505. [355] (a) * * *

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(4) A new drug manufactured in a pilot or other small facility may be used to demonstrate the safety and effectiveness of the new drug and to obtain approval of the new drug prior to scaling up to a larger facility, unless the Secretary determines that a full scale production facility is necessary to ensure the safety or effectiveness of the new drug.

* * * * * * *

(d) If the Secretary finds, after due notice to the applicant in accordance with subsection (c) and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b), do not include adequate tests by

all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) the application failed to contain the patent information prescribed by subsection (b); or (7) bad on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve he application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e), the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of used prescribed, recommended, or suggested in the labeling or proposed labeling thereof. *Substantial evidence may, as appropriate, consist of data from 1 adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation), if the Secretary determines, based on relevant science, that such data and evidence are sufficient to establish effectiveness.*

* * * * * * *

(n) The provisions of subsections (a) and (j) shall not apply to the preparation of a compounded positron emission tomography drug.

SEC. 505A. PEDIATRIC STUDIES OF DRUGS.

(a) MARKET EXCLUSIVITY FOR NEW DRUGS.—If, prior to approval of an application that is submitted under section 505(b)(1) the Secretary determines that information relating to the use of a drug in the pediatric population may produce health benefits in that population, the Secretary makes a written request for pediatric studies (which may include a timeframe for completing such studies), and such studies are completed within any such timeframe and the reports thereof submitted in accordance with subsection (d)(2) or completed within any such timeframe and the reports thereof are accepted in accordance with subsection (d)(3)—

(1)(A) the period during which an application may not be submitted under subsections (c)(3)(D)(ii) and (i)(4)(D)(ii) of sec-

tion 505 shall be five years and six months rather than five years, and the references in subsections (c)(3)(D)(ii) and (j)(4)(D)(ii) of section 505 to four years, to forty-eight months, and to seven and one-half years shall be deemed to be four and one-half years, fifty-four months, and eight years, respectively; or

(B) the period of market exclusivity under subsections (c)(3)(D) (iii) and (iv) and (j)(4)(D) (iii) and (iv) of section 505 shall be three years and six months rather than three years; and

(2)(A) if the drug is the subject of—

(i) a listed patent for which a certification has been submitted under section 505(b)(2)(A)(ii) or section (j)(2)(A)(vii)(II) and for which pediatric studies were submitted prior to the expiration of the patent (including any patent extensions); or

(ii) a listed patent for which a certification has been submitted under section 505(b)(2)(A(iii) or section 505(j)(2)(A)(vii)(III),

the period during which an application may not be approved under section 505(c)(3) or section 505(j)(4)(B) shall be extended by a period of six months after the date the patent expires (including any patent extensions); or

(B) if the drug is the subject of a listed patent for which a certification has been submitted under section 505(b)(2)(A)(iv) or section 505(j)(2)(A)(vii)(IV), and in the patent infringement litigation resulting from the certification the court determines that the patent is valid and would be infringed, the period during which an application may not be approved under section 505(c)(3) or section 505(j)(4)(B) shall be extended by a period of six months after the date the patent expires (including any patent extensions).

(b) SECRETARY TO DEVELOP LIST OF DRUGS FOR WHICH ADDITIONAL PEDIATRIC INFORMATION MAY BE BENEFICIAL.—Not later than 180 days after the date of enactment of this section, the Secretary, after consultation with experts in pediatric research (such as the American Academy of Pediatrics, the Pediatric Pharmacology Research Unit Network, and the United States Pharmacopoeia) shall develop, prioritize, and publish an initial list of approved drugs for which additional pediatric information may produce health benefits in the pediatric population. The Secretary shall annually update the list.

(c) MARKET EXCLUSIVITY FOR ALREADY-MARKETED DRUGS.—If the Secretary makes a written request for pediatric studies (which may include a timeframe for completing such studies) concerning a drug identified in the list described in subsection (b) to the holder of an approved application under section 505(b)(1) for the drug, the holder agrees to the request, and the studies are completed within any such timeframe and the reports thereof submitted in accordance with subsection (d)(2) or completed within any such timeframe and the reports thereof accepted in accordance with subsection with subsection (d)(3)—

(1)(A) the period during which an application may not be submitted under subsections (c)(3)(D)(ii) and (j)(4)(D)(ii) of sec-

tion 505 shall be five years and six months rather than five years, and the references in subsections (c)(3)(D)(ii) and (j)(4)(D)(ii) of section 505 to four years, to forty-eight months, and to seven and one-half years shall be deemed to be four and one-half years, fifty-four months, and eight years, respectively; or

(B) the period of market exclusively under subsections (c)(3)(D) (iii) and (iv) and (j)(4)(D) (iii) and (iv) of section 505 shall be three years and six months rather than three years; and

(2)(A) if the drug is the subject of—

(i) listed patent for which a certification has been submitted under section 505(b)(2)(A)(ii) or (j)(2)(A)(vii)(II) and for which pediatric studies were submitted prior to the expiration of the patent (including any patent extensions); or

(ii) a listed patent for which a certification has been submitted under section 505(b)(2)(A)(iii) or section 505(j)(2)(A)(vii)(III),

the period during which an application may not be approved under section 505(c)(3) or section 505(j)(4)(B) shall be extended by a period of six months after the date the patent expires (including any patent extensions); or

(B) if the drug is the subject of a listed patent for which a certification has been submitted under section 505(b)(2)(A)(iv) or section 505(j)(2)(A)(vii)(IV), and in the patent infringement litigation resulting from the certification the court determines that the patent is valid and would be infringed, the period during which an application may not be approved under section 505(c)(3) or section 505(j)(4)(B) shall be extended by a period of six months after the date the patent expires (including any patent extensions).

(d) CONDUCT OF PEDIATRIC STUDIES.—

(1) AGREEMENT FOR STUDIES.—The Secretary may, pursuant to a written request for studies, after consultation with—

(A) the sponsor of an application for an investigational new drug under section 505(i);

(B) the sponsor of an application for a drug under section 505(b)(1); or

(C) the holder of an approved application for a drug under section 505(b)(1),

agree with the sponsor or holder for the conduct of pediatric studies for such drug.

(2) WRITTEN PROTOCOLS TO MEET THE STUDIES REQUIREMENT.—If the sponsor or holder and the Secretary agree upon written protocols for the studies, the studies requirement of subsection (a) or (c) is satisfied upon the completion of the studies and submission of the reports thereof in accordance with the original written request and the written agreement referred to in paragraph (1). Not later than 60 days after the submission of the report of the studies, the Secretary shall determine if such studies were or were not conducted in accordance with the original written request and the written agreement and reported in accordance with the requirements of the Secretary for filing and so notify the sponsor or holder.

(3) OTHER METHODS TO MEET THE STUDIES REQUIREMENT.—If the sponsor or holder and the Secretary have not agreed in writing on the protocols for the studies, the studies requirement of subsection (a) or (c) is satisfied when such studies have been completed and the reports accepted by the Secretary. Not later than 90 days after the submission of the reports of the studies, the Secretary shall accept or reject such reports and so notify the sponsor or holder. The Secretary's only responsibility in accepting or rejecting the reports shall be to determine, within the 90 days, whether the studies fairly respond to the written request, whether such studies have been conducted in accordance with commonly accepted scientific principles and protocols, and whether such studies have been reported in accordance with the requirements of the Secretary for filing.

(e) DELAY OF EFFECTIVE DATE FOR CERTAIN APPLICATIONS; PERIOD OF MARKET EXCLUSIVITY.—If the Secretary determines that the acceptance or approval of an application under section 505(b)(2) or 505(j) for a drug may occur after submission of reports of pediatric studies under this section, which were submitted prior to the expiration of the patent (including any patent extension) or market exclusivity protection, but before the Secretary has determined whether the requirements of subsection (d) have been satisfied, the Secretary shall delay the acceptance or approval under section 505(b)(2) or 505(j), respectively, until the determination under subsection (d) is made, but such delay shall not exceed 90 days. In the event that requirements of this section are satisfied, the applicable period of market exclusivity referred to in subsection (a) or (c) shall be deemed to have been running during the period of delay.

(f) NOTICE OF DETERMINATION ON STUDIES REQUIREMENTS.—The Secretary shall publish a notice of any determination that the requirements of subsection (d) have been met and that submissions and approvals under section 505(b)(2) or (j) for a drug will be subject to the provisions of this section.

(g) DEFINITIONS.—As used in this section, the term "pediatric studies" or "studies" means at least 1 clinical investigation (that, at the Secretary's discretion, may include pharmacokinetic studies) in pediatric age-groups in which a drug is anticipated to be used.

(h) LIMITATION.—The holder of an approved application for a new drug that has already received six months of market exclusivity under subsection (a) or (c) may, if otherwise eligible, obtain six months of market exclusivity under subsection (c)(1)(B) for a supplemental application, except that the holder is not eligible for exclusivity under subsection(c)(2).

(i) SUNSET.—No period of market exclusivity shall be granted under this section based on studies commenced after January 1, 2004. The Secretary shall conduct at study and report to Congress not later than January 1, 2003 based on the experience under the program. The study and report shall examine all relevant issues, including—

(1) the effectiveness of the program in improving information about important pediatric uses for approved drugs;

(2) the adequacy of the incentive provided under this section;

(3) the economic impact of the program; and

(4) any suggestions for modification that the Secretary deems appropriate.

* * * * * * *

REGISTRATION OF PRODUCERS OF DRUGS AND DEVICES

SEC. 510. [360] (a) As used in this section—

* * * * * * *

(4) any distributor who acts as a wholesale distributor of devices, and who does not manufacture, repackage, process, or relabel a device; or

[4] *(5)* such other classes of persons as the Secretary may be regulation exempt from the application of this section upon a finding that registration by such classes of persons in accordance with this section is not necessary for the protection of the public health.

In this subsection, the term "wholesale distributor" means any person who distributes a device from the original place of manufacture to the person who makes the final delivery or sale of the device to the ultimate consumer or user.

* * * * * * *

[(i) Any establishment within any foreign country engaged in the manufacture, preparation, propagation, compounding, or processing of a drug or drugs or a device or devices, shall be permitted to register under this section pursuant to regulations promulgated by the Secretary. Such regulations shall require such establishment to provide the information required by section (j) and shall require such establishment to provide information required by subsection (j) in the case of a device or devices and shall include provisions for registration of any such establishment upon condition that adequate and effective means are available, by arrangement with the government of such foreign country or otherwise, to enable the Secretary to determine from time to time whether drugs or devices manufactured, prepared, propagated, compounded, or processed in such establishment, if imported or offered for import into the United States, shall be refused admission on any of the grounds set forth in section 801(a) of this Act.]

(i)(1) Any establishment within any foreign country engaged in the manufacture, preparation, propagation, compounding, or processing of a drug or a device that is imported or offered for import into the United States shall register with the Secretary the name and place of business of the establishment and the name of the United States agent for the establishment.

(2) The establishment shall also provide the information required by subsection (j).

(3) The Secretary is authorized to enter into cooperative arrangements with foreign countries to ensure that adequate and effective means are available for purposes of determining, from time to time, whether drugs or devices manufactured, prepared, propagated, compounded, or processed by an establishment described in paragraph (1), if imported or offered for import into the United States,

shall be refused admission on any of the grounds set forth in section 801(a).

* * * * * * *

(k) Each person who is required to register under this section and who proposes to begin the introduction or delivery for introduction into interstate commerce for commercial distribution of a device [intended for human use] *intended for human use (except a device that is classified into class I under section 513 or 520 unless the Secretary determines such device is intended for a use which is of substantial importance in preventing impairment of human health, or presents a potential unreasonable risk of illness or injury, or a device that is classified into class II under section 513 or 520 and is exempt from the requirements of this subsection under subsection (l))* shall, at least ninety days before making such introduction or delivery, report to the Secretary (in such form and manner as the Secretary shall by regulation prescribe—

* * * * * * *

The Secretary shall review the notification required by this subsection and make a determination under section 513(f)(1) not later than 90 days after receiving the notification.

(l)(1) Not later than 30 days after the date of enactment of this subsection, the Secretary shall publish in the Federal Register a list of each type of class II device that does not require a notification under subsection (k) to provide reasonable assurance of safety and effectiveness. Each type of class II device identified by the Secretary not to require the notification shall be exempt from the requirement to provide notification under subsection (k) as of the date of the publication of the list in the Federal Register.

(2) Beginning on the date that is 1 day after the date of the publication of a list under this subsection, the Secretary may exempt a class II device from the notification requirement subsection (k), upon the Secretary's own initiative or a petition of an interested person, if the Secretary determines that such notification is not necessary to assure the safety and effectiveness of the device. The Secretary shall publish in the Federal Register notice of the intent of the Secretary to exempt the device, or of the petition, and provide a 30-day comment period for public comment. Within 120 days after the issuance of the notice in the Federal Register, the Secretary shall publish an order in the Federal Register that sets forth the final determination of the Secretary regarding the exemption of the device that was the subject of the notice.

(m)(l) The Secretary may not withhold a determination of the initial classification of a device under section 513(f)(1) because of a failure to comply with any provision of this Act that is unrelated to a substantial equivalence decision, including a failure to comply with the requirements relating to good manufacturing practices under section 520(f).

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CLASSIFICATION OF DEVICES INTENDED FOR HUMAN USE

Device Classes

SEC. 513 [360c] (a)(1) * * *

* * * * * * *

(3)(A) Except as authorized by subparagraph (B), the effectiveness of a device is, for purposes of this section and sections 514 and 515, to be determined, in accordance with regulations promulgated by the Secretary, on the basis of well-controlled investigations, including [clinical investigations] *1 or more clinical investigations* where appropriate, by experts qualified by training and experience to evaluate the effectiveness of the device, from which investigations it can fairly and responsibly be concluded by qualified experts that the device will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling of the device.

* * * * * * *

(C)(i)(I) The Secretary, upon the written request of any person intending to submit an application under section 515, shall meet with such person to determine the type of valid scientific evidence (within the meaning of subparagraphs (A) and (B)) that will be necessary to demonstrate the effectiveness of a device for the conditions of use proposed by such person, to support an approval of an application. The written request shall include a detailed description of the device, a detail description of the proposed conditions of use of the device, and, if available, information regarding the expected performance from the device. Within 30 days after such meeting, the Secretary shall specify in writing the type of valid scientific evidence that will provide a reasonable assurance that a device is effective under the conditions of use proposed by such person.

(II) Any clinical data, including 1 or more well-controlled investigations, specified in writing by the Secretary for demonstrating a reasonable assurance of device effectiveness shall be specified as a result of a determination by the Secretary—

(aa) that such data are necessary to establish device effectiveness; and

(bb) that no other less burdensome means of evaluating device effectiveness is available that would have a reasonable likelihood of resulting in an approval.

(ii) The determination of the Secretary with respect to the specification of valid scientific evidence under clause (i) shall be binding upon the Secretary, unless—

(I) such determination by the Secretary would be contrary to the public health; or

(II) based on new information (other than the information reviewed by the Secretary in making such determination) obtained by the Secretary prior to the approval of an application for an investigational device exemption under section 520(g), the Secretary finds that such determination is scientifically inappropriate.

* * * * * * *

(f)(1) * * *

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(B) the Secretary in response to a petition submitted under [paragraph (2)] *paragraph (3)* has classified such device in class I or II.

A device classified in class III under this paragraph shall be classified in that class until the effective date of an order of the Secretary under [paragraph (2)] *paragraph (2) or (3)* classifying the device in class I or II.

(2)(A) Any person who submits a report under section 510(k) for a type of device that has not been previously classified under this Act, and that is classified into class III under paragraph (1), may request, within 30 days after receiving written notice of such a classification, the Secretary to classify the device into class I or II under the criteria set forth in subparagraphs (A) through (C) subsection (a)(1). The person may, in the request, recommend to the Secretary a classification for the device. The request shall describe the device and provide detailed information and reasons for the recommended classification.

(B)(i) Not later than 60 days after the date of the submission of the request under subparagraph (A) for classification of a device under the criteria set forth in subparagraphs (A) through (C) of subsection (a)(1), the Secretary shall by written order classify the device. Such classification shall be the initial classification of the device for purposes of paragraph (1) and any device classified under this paragraph into class I or II shall be a predicate device for determining substantial equivalence under paragraph (1).

(ii) A device that remains in class III under this subparagraph shall be deemed to be adulterated with the meaning of section 501(f)(B) until approved under section 515 or exempted from such approval under section 520(g).

(C) Within 30 days after the issuance of an order classifying a device under this paragraph, the Secretary shall publish a notice in the Federal Register announcing such classification.

[(2)] *(3)*(A) The Secretary may initiate the reclassification of a device classified into class III under paragraph (1) of this subsection or the manufacturer or importer of a device classified under paragraph (1) may petition the Secretary (in such form and manner as he shall prescribe) for the issuance of an order classifying the device in class I or class II. Within thirty days of the filing of such a petition, the Secretary shall notify the petitioner for any deficiencies in the petition which prevent the Secretary from making a decision on the petition.

* * * * * * *

[(3)] *(4)* If a manufacturer reports to the Secretary under section 510(k) that a device is substantially equivalent to another device—

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(C) Whenever the Secretary requests information to demonstrate that the devices with differing technological characteristics are substantially equivalent, the Secretary shall only request information that is necessary to make a substantial equivalence determination. In making such a request, the Sec-

retary shall consider the least burdensome means of demonstrating substantial equivalence and shall request information accordingly.

(D) The determinations of the Secretary under this section and section 513(f)(1) with respect to the intended use of a device shall be based on the intended use included in proposed labeling of the device submitted in a report under section 510(k).

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PERFORMANCE STANDARDS

Provisions of Standards

SEC. 514. [360d] (a)(1) * * *

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Recognition of a Standard

(c)(1)(A) In addition to establishing performance standards under this section, the Secretary may, by publication in the Federal Register recognize all or part of a performance standard established by a nationally or internationally recognized standard development organization for which a person may submit a declaration of conformity in order to meet premarket submission requirements or other requirements under this Act to which such standards are applicable.

(B) If a person elects to use a performance standard recognized by the Secretary under subparagraph (A) to meet the requirements described in subparagraph (A), the person shall provide a declaration of conformity to the Secretary that certifies that the device is in conformity with such standard. A person may elect to use data, or information, other than data required by a standard recognized under subparagraph (A) to fulfill or satisfy any requirement under this Act.

(2) The Secretary may withdraw such recognition of a performance standard through publication of a notice in the Federal Register that the Secretary will no longer recognize the standard, if the Secretary determines that the standard is no longer appropriate for meeting the requirements under this Act.

(3)(A) Subject to subparagraph (B), the Secretary shall accept a declaration of conformity that a device is in conformity with a standard recognized under paragraph (1) unless the Secretary finds—

(i) that the data or information submitted to support such declaration does not demonstrate that the device is in conformity with the standard identified in the declaration of conformity; or

(ii) that the standard identified in the declaration of conformity is not applicable to the particular device under review.

(B) The Secretary may request, at any time, the data or information relied on by the person to make a declaration of conformity with respect to a standard recognized under paragraph (1).

(C) A person relying on a declaration of conformity with respect to a standard recognized under paragraph (1) shall maintain the data and information demonstrating conformity of the device to the standard for a period of 2 years after the date of the classification

or approval of the device by the Secretary or a period equal to the expected design life of the device, whichever is longer.

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PREMARKET APPROVAL

General Requirement

SEC. 515. [360e] (a) A class III device—

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Action on an Application for Premarket Approval

(d)(1)(A) * * *

* * * * * * *

(i) issue an order approving the application if he finds that none of the grounds for denying approval specified in [paragraph (2) of this subsection] *paragraph 4* applies; or

(ii) deny approval of the application if he finds (and sets forth the basis for such finding as part of or accompanying such denial) that one or more grounds for denial specified in [paragraph (2) of this subsection] *paragraph 4* apply.

In making the determination whether to approve or deny an application, the Secretary shall rely on the conditions of use proposed in the labeling of a device as the basis for determining whether or not there is a reasonable assurance of safety and effectiveness. If, based on a fair evaluation of all material facts, the proposed labeling is neither false nor misleading in any particular, the Secretary, in making the determination, shall not consider conditions of use not included in the proposed labeling.

(2)(A)(i) The Secretary shall, upon the written request of the applicant involved, meet with the applicant not later than 100 days after the receipt of an application, from the applicant, that has been filed as complete under subsection (c), to discuss the review status of the application.

(ii) If the application does not appear in a form that would require an approval under this subsection, the Secretary shall in writing, and prior to the meeting, provide to the applicant a description of any deficiencies in the application identified by the Secretary and identify the information (other than information the Secretary needs to make a finding under paragraph (4)(C)) that is required to bring the application into an approvable form.

(iii) The Secretary and the applicant may, by mutual consent, establish a different schedule for a meeting required under this paragraph.

(B) The Secretary shall notify the applicant immediately of any deficiency identified in the application that was not described as a deficiency in the written description provided by the Secretary under subparagraph (A).

(3) Except as provided in paragraph (1), the period for the review of an application by the Secretary under this subsection shall be not

more than 180 days. Such period may not be restarted or extended even if the application is amended.

[(2)**]** *(4)* The Secretary shall deny approval of an application for a device if, upon the basis of the information submitted to the Secretary as part of the application and any other information before him with respect to such device, the Secretary finds that—

* * * * * * *

[(3)**]** *(5)* An applicant whose application has been denied approval may, by petition filed on or before the thirtieth day after the date upon which he receives notice of such denial, obtain review thereof in accordance with either paragraph (1) or (2) of subsection (g), and any interested person may obtain review, in accordance with paragraph (1) or (2) of subsection (g), of an order of the Secretary approving an application.

* * * * * * *

(iii) The Secretary shall accept and review data and any other information from investigations conducted under the authority of regulations required by section 520(g), to make a determination of whether there is a reasonable assurance of safety and effectiveness of a device subject to a pending application under this section if—

(I) the data or information is derived from investigations of an earlier version of the device, the device has been modified during or after the investigations (but prior to submission of an application under subsection (c)) and such a modification of the device does not constitute a significant change in the design or in the basic principles of operation of the device that would invalidate the data or information; or

(II) the data or information relates to a device approved under this section, is available for use under this Act, and is relevant to the design and intended use of the device for which the application is pending.

* * * * * * *

(6)(A)(i) A supplemental application shall be required for any change to a device subject to an approved application under this subsection that affects safety or effectiveness, unless such change is a modification in a manufacturing procedure or method of manufacturing and the holder of the approved application submits a written notice to the Secretary that describes in detail the change, summarizes the data or information supporting the change, and informs the Secretary that the change has been made under the requirements of section 520(f).

(ii) The holder of an approved application who submits a notice under clause (i) with respect to a manufacturing change of a device shall not distribute the device for a period of 14 days after the date on which the Secretary receives the notice.

(B)(i) Subject to clause (ii), in reviewing a supplement to an approved application, for an incremental change to the design of a device that affects safety or effectiveness, the Secretary shall approve such supplement if—

(I) nonclinical data demonstrate that the design modification creates the intended additional capacity, function, or performance of the device; and

(II) clinical data from the approved application and any supplement to the approval application provide a reasonable assurance of safety and effectiveness for the changed device.

(ii) The Secretary may require, when necessary, additional clinical data to evaluate the design modification to provide a reasonable assurance of safety and effectiveness.

* * * * * * *

JUDICIAL REVIEW

Application of Section

SEC. 517. [360g] (a) Not later than thirty days after—

* * * * * * *

(8) an order pursuant to section 513(i), *or*

(9) a regulation under section 515(i)(2) or 520(l)(5)(B)[, or],

[(10) an order under section 520(h)(4)(B),]

* * * * * * *

NOTFICATION AND OTHER REMEDIES

Notification

SEC. 518. (a) If the Secretary determines that—

* * * * * * *

Recall Authority

(e)(1) * * *

* * * * * * *

(2)(A) If, after providing an opportunity for an informal hearing under paragraph (1), the Secretary determines that the order should be amended to include a recall of the device with respect to which the order was issued, the Secretary shall, except as provided in [subparagraphs (B) and (C)] *subparagraph (B)*, amend the order to require a recall. The Secretary shall specify a timetable in which the device recall will occur and shall require periodic reports to the Secretary describing the progress of the recall.

* * * * * * *

(C) If the Secretary issues an amended order under subparagraph (A), the Secretary may require the person subject to the order to submit such samples of the device and of components of the device as the Secretary may reasonably require. If the submission of such samples is impracticable or unduly burdensome, the requirement of this subparagraph may be met by the submission of complete information concerning the location of 1 or more such devices readily available for examination and testing.

* * * * * * *

RECORDS AND REPORTS ON DEVICES

General Rule

SEC. 519. [360i] (a) Every person who is a manufacturer, importer, or distributor of a device intended for human use shall establish and maintain such records, [make such reports, and provide such information,] *and submit such samples and components of devices (as required by paragraph (10)),* as the Secretary may by regulation reasonably require to assure that such device is not adulterated or misbranded and to otherwise assure its safety and effectiveness. *Every person who is a manufacturer or importer of a device intended for human use shall make reports, and provide such information, as the Secretary may by regulation reasonably require to assure that such device is not adulterated or misbranded and to assure the safety and effectiveness of such device.* Regulations prescribed under the preceding [sentence] *sentences*—

* * * * * * *

(8) may not require a manufacturer, importer, or distributor of a class I device to—

(A) maintain for such device records respecting information not in the possession of the manufacturer, importer, or distributor, or

(B) to submit for such a device to the Secretary any report or information—

(i) not in the possession of the manufacturer, importer, or distributor, or

(ii) on a periodic basis,

unless such report or information is necessary to determine if the device should be reclassified or if the device is adulterated or misbranded[; and];

[(9) shall require distributors who submit such reports to submit copies of the reports to the manufacturer of the device for which the report was made.]

(9) shall require distributors to keep records and make such records available to the Secretary upon request; and

(10) may reasonably require a manufacturer, importer, or distributor to submit samples of a device and of components of the device that may have caused or contributed to a death or serious injury, except that if the submission of such samples is impracticable or unduly burdensome, the requirement of this paragraph may be met by the submission of complete information concerning the location of 1 or more such devices readily available for examination and testing.

[Certification

[(d) Each manufacturer, importer, and distributor required to make reports under subsection (a) shall submit to the Secretary annually a statement certifying that—

[(1) the manufacturer, importer, or distributor did file a certain number of such reports, or

[(2) the manufacturer, importer, or distributor did not file any report under subsection (a).]

* * * * * * *

Reports of Removals and Corrections

(f)(1) Except as provided in paragraph (2), the Secretary shall by regulation require a manufacturer[, importer, or distributor] *or importer* of a device to report promptly to the Secretary any correction or removal of a device undertaken by such manufacturer, importer, or distributor if the removal or correction was undertaken—

(A) to reduce the risk to health posed by the device, or

(B) to remedy a violation of this Act caused by the device which may present a risk to health.

A manfacturer[, importer, or distributor] *or importer* of a device who undertakes a correction or removal of a device which is not required to be reported under this paragraph shall keep a record of such correction or removal.

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(e) * * *

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Any patient receiving a device subject to tracking under this section may refuse to release, or refuse permission to release, the patient's name, address, social security number, or other identifying information for the purpose of tracking.

* * * * * * *

GENERAL PROVISIONS RESPECTING CONTROL OF DEVICES INTENDED FOR HUMAN USE

General Rule

SEC. 520. [360j] (a) * * *

* * * * * * *

(6)(A) The Secretary shall, not later than 120 days after the date of enactment of this paragraph, by regulation modify parts 812 and 813 of title 21, Code of Federal Regulations to update the procedures and conditions under which a device intended for human use may, upon application by the sponsor of the device, be granted an exemption from the requirements of this Act.

(B) The regulation shall permit developmental changes in a device (including manufacturing changes) in response to information collected during an investigation without requiring an additional approval of an application for an investigational device exemption or the approval of a supplemental to such application, if the sponsor of the investigation determines, based on credible information, prior to making any such changes, that the changes—

(i) do not affect the scientific soundness of an investigational plan submitted under paragraph (3)(A) or the rights, safety, or welfare of the human subjects involved in the investigation; and

(i) do not constitute a significant change in design, or a significant change in basis principles of operation, of the device.

[(4)(A) Any information contained in an application for premarket approval filed with the Secretary pursuant to section 515(c), including clinical and preclinical tests or studies, but excluding descriptions of methods of manufacture and product composition, that demonstrates the safety and effectiveness of a device shall be available 1 year after the original application for the fourth device of a kind has been approved by the Secretary, for use by the Secretary in approving devices, or determining whether a product development protocol has been completed, under section 515, establishing a performance standard under section 514, and reclassifying devices under subsections (e) and (f) of section 513, and subsection (l)(2). The Secretary shall deem devices that incorporate the same technologies, have the same principles of operation, and are intended for the same use or uses to be within a kind of device.]

(4)(A) Any information contained in an application for premarket approval filed with the Secretary pursuant to section 515(c) (including information from clinical and preclinical tests or studies that demonstrate the safety and effectiveness of a device, but excluding descriptions of methods of manufacture and product composition) shall be available, 6 years after the application has been approved by the Secretary, for use by the Secretary in—

(i) approving another device;

(ii) determining whether a product development protocol has been completed, under section 515 for another device;

(iii) establishing a performance standard or special control under section 514 for another device; and

(iv) classifying or reclassifying another device under section 513 and subsection (l)(2).

(B) The publicly available detailed summaries of information respecting the safety and effectiveness of devices required by paragraph (l)(A) shall be available for use by the Secretary as the evidentiary basis for the agency action described in subparagraph (A).

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GENERAL PROVISIONS RESPECTING CONTROL OF DEVICES INTENDED FOR HUMAN USE

General Rule

SEC. 520. [360j] (a) * * *

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(m)(1) * * *

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The request shall be in the form of an application submitted to the Secretary. Not later than 60 days after the date of the receipt

of the application, the Secretary shall issue an order approving or denying the application.

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(4) Devices granted an exemption under paragraph (2) may only be used—

* * * * * * *

(B) if, before the use of a device, an institutional review committee approves the use in the treatment or diagnosis of a disease or condition referred to in paragraph (2)(A)*, unless a physician determines that waiting for such an approval from an institutional review committee will cause harm or death to a patient, and makes a good faith effort to obtain the approval, and does not receive a timely response from an institutional review committee on the request of the physician for approval to use the device for such treatment or diagnosis.*

In a case in which a physician described in subparagraph (B) uses a device without an approval from an institutional review committee, the physician shall, after the use of the device, notify the chairperson of the institutional review committee of such use. Such notification shall include the identification of the patient involved, the date on which the device was used, and the reason for the use.

* * * * * * *

[(5) An exemption under paragraph (2) shall be for a term of 18 months and may only be initially granted in the 5-year period beginning on the date regulations under paragraph (6) take effect. The Secretary may extend such an exemption for a period of 18 months if the Secretary is able to make the findings set forth in paragraph (2) and if the applicant supplies information demonstrating compliance with paragraph (3). An exemption may be extended more than once and may be extended after the expiration of such 5-year period.**]**

(5) The Secretary may require a person granted an exemption under paragraph (2) to demonstrate continued compliance with the requirements of this subsection if the Secretary believes such demonstration to be necessary to protect the public health or if the Secretary has reason to believe that the criteria for the exemption are no longer met.

* * * * * * *

POSTMARKET SURVEILLANCE

[SEC. 522. **[**3601**]** (a) IN GENERAL.—

(1) REQUIRED SURVEILLANCE.—The Secretary shall require a manufacturee to conduct postmarket surveillance for any device of the manufacturer first introduced or delivered for introduction into interstate commerce after January 1, 1991, that—

(A) is a permanent implant the failure of which may cause serious, adverse health consequences or death,

(B) is intended for a use in supporting or sustaining human life, or

(C) potentially presents a serious risk to human health.

(2) DISCRETIONARY SURVEILLANCE.—The] *SEC. 522. (a) DISCRETIONARY SURVEILLANCE.—The* Secretary may require a manufacturer to conduct postmarket surveillance for a device of the manufacturer if the Secretary determines that postmarket surveillance of the device is necessary to protect the public health or to provide safety or effectiveness data for the device.

[(b) SURVEILLANCE APPROVAL.—Each manufacturer required to conduct a surveillance of a device under subsection (a)(1) shall, within 30 days of the first introduction or delivery for introduction of such device into interstate commerce, submit, for the approval of the Secretary, a protocol for the required surveillance. Each manufacturer required to conduct a surveillance of a device under subsection (a)(2) shall within 30 days after receiving notice that the manufacturer is required to conduct such surveillance, submit, for the approval of the Secretary, a protocol for the required surveillance. The Secretary, within 60 days of the receipt of such protocol, shall determine if the principal investigator proposed to be used in the surveillance has sufficient qualifications and experience to conduct such surveillance and if such protocol will result in collection of useful data or other information necessary to protect the public health and to provide safety and effectiveness information for the device. The Secretary may not approve such a protocol until it has been reviewed by an appropriately qualified scientific and technical review committee established by the Secretary.]

(b) SURVEILLANCE APPROVAL.—

(1) IN GENERAL.—Each manufacturer that receives notice from the Secretary that the manufacturer is required to conduct surveillance of a device under subsection (a) shall, not later than 30 days after receiving the notice, submit for the approval of the Secretary, a plan for the required surveillance.

(2) DETERMINATION.—Not later than 60 days after the receipt of the plan, the Secretary shall determine if a person proposed in the plan to conduct the surveillance has sufficient qualifications and experience to conduct the surveillance and if the plan will result in the collection of useful data that can reveal unforeseen adverse events or other information necessary to protect the public health and to provide safety and effectiveness information for the device.

(3) LIMITATION ON PLAN APPROVAL.—The Secretary may not approve the plan until the plan has been reviewed by a qualified scientific and technical review committee established by the Secretary.

(c) DURATION OF SURVEILLANCE.—

(1) IN GENERAL.—Each manufacturer required to conduct surveillance of a device under subsection (a) shall be required to conduct such surveillance for not longer than 24 months.

(2) EXTENSION OF THE PERIOD OF SURVEILLANCE.—If the Secretary determines that additional surveillance is needed to identify the incidence of adverse events documented during the initial period of surveillance that were not foreseen at the time of approval or classification of the device, the Secretary may extend the period of surveillance for such time as may be necessary after providing the person required to conduct such sur-

veillance an opportunity for an informal hearing to determine whether or not additional surveillance is appropriate and to determine the appropriate period, if any, for such surveillance.

* * * * * * *

SEC. 523. ACCREDITED-PARTY PARTICIPATION.

(a) ACCREDITATION.—

(1) IN GENERAL.—Not later than 1 year after the date of enactment of this section, the Secretary shall accredit entities or individuals who are not employees of the Federal Government, to review reports made to the Secretary under section 510(k) for devices and make recommendations to the Secretary regarding the initial classification of such devices under section 513(f)(1), except that this paragraph shall not apply to reports made to the Secretary under section 510(k) for devices that are—

(A) life-supporting;

(B) life sustaining; or

(C) intended for implantation in the human body for a period of over 1 year.

(2) SPECIAL RULE.—The Secretary shall have the discretion to accredit entities or individuals who are not employees of the Federal Government—

(A) to review reports made to the Secretary under section 510(k) for devices described in subparagraphs (A) through (C) of paragraph (1), and make recommendations of initial classification of such devices; or

(B) to review applications for premarket approval for class III devices under section 515 and make recommendations with respect to the approval or disapproval of such applications.

(b) ACCREDITATION.—Within 180 days after the date of enactment of this section, the Secretary shall adopt methods of accreditation that ensure that entities or individuals who conduct reviews and make recommendations under this section are qualified, properly trained, knowledgeable about handling confidential documents and information, and free of conflicts of interest. The Secretary shall publish the methods of accreditation in the Federal Register on the adoption of the methods.

(c) WITHDRAWAL OF ACCREDITATION.—The Secretary may suspend or withdraw the accreditation of any entity or individual accredited under this section, after providing notice and an opportunity for an informal hearing, if such entity or individual acts in a manner that is substantially not in compliance with the requirements established by the Secretary under subsection (b), including the failure to avoid conflicts of interest, the failure to protect confidentiality of information, or the failure to competently review premarket submissions for devices.

(d) SELECTION AND COMPENSATION.—Subject to subsection (a)(2), a person who intends to make a report described in subsection (a), or to submit an application described in subsection (a), to the Secretary shall have the option to select an accredited entity or individual to review such report or application. Upon the request by a person to have a report or application reviewed by an accredited entity or individual, the Secretary shall identify for the person no less

than 2 accredited entities or individuals from whom the selection may be made. Compensation for an accredited entity or individual shall be determined by agreement between the accredited entity or individual and the person who engages the services of the accredited entity or individual and shall be paid by the person who engages such services.

(e) REVIEW BY SECRETARY.—

(1) IN GENERAL.—The Secretary shall require an accredited entity or individual, upon making a recommendation under this section with respect to an initial classification of a device or approval or disapproval of an application for premarket approval, to notify the Secretary in writing of the reasons for such recommendation.

(2) TIME PERIOD FOR REVIEW.—

(A) INITIAL CLASSIFICATION.—Not later than 30 days after the date on which the Secretary is notified under paragraph (1) by an accredited entity or individual with respect to a recommendation of an initial classification of a device, the Secretary shall make a determination with respect to the initial classification.

(B) PREMARKET APPROVAL.—Not later than 60 days after the date on which the Secretary is notified under paragraph (1) by an accredited entity or individual with respect to a recommendation of an approval or disapproval of an application for a device, the Secretary shall make a determination with respect to the approval or disapproval.

(3) SPECIAL RULE.—The Secretary may change the initial classification under section 513(f)(1), or the approval or disapproval of the application under section 515(d), that is recommended by the accredited entity or individual under this section, and in such case shall notify in writing the person making the report or application described in subsection (a) of the detailed reasons for the change.

(f) DURATION.—The authority provided by this section terminates—

(1) 5 years after the date on which the Secretary notifies Congress that at least 2 persons accredited under subsection (b) are available to review devices for each of at least 70 percent of the generic types of devices subject to review under subsection (a); or

(2) 4 years after the date on which the Secretary notifies Congress that at least 35 percent of the devices that are subject to review under subsection (a), and that were the subject of final action by the Secretary in the fiscal year preceding the date of such notification, were reviewed by the Secretary under subsection (e),

whichever occurs first.

(g) REPORT.—

(1) IN GENERAL.—Not later than 1 year after the date of enactment of this section, the Secretary shall contract with an independent research organization to prepare and submit to the Secretary a written report examining the use of accredited entities and individuals to conduct reviews under this section. The Secretary shall submit the report to Congress not later than 6

months prior to the conclusion of the applicable period described in subsection (f).

(2) CONTENTS.—The report by the independent research organization described in paragraph (1) shall identify the benefits or detriments to public and patient health of using accredited entities and individuals to conduct such reviews, and shall summarize all relevant data, including data on the review of accredited entities and individuals (including data on the review times, recommendations, and compensation of the entities and individuals), and data on the review of the Secretary (including data on the review times, changes, and reasons for changes of the Secretary).

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SUBCHAPTER D—UNAPPROVED THERAPIES AND DIAGNOSTICS

SEC. 551. EXPANDED ACCESS TO UNAPPROVED THERAPIES AND DIAGNOSTICS.

(a) IN GENERAL.—Any person, acting through a physician licensed in accordance with State law, may request from a manufacturer or distributor, and any manufacturer or distributor may provide to a person after compliance with the provisions of this section, an investigational drug (including a biological product) or investigational device for the diagnosis, monitoring, or treatment of a serious disease or condition, or any other disease or condition designated by the Secretary as appropriate for expanded access under this section if—

(1) the licensed physician determines that the person has no comparable or satisfactory alternative therapy available to diagnose, monitor, or treat the disease or condition involved;

(2) the licensed physician determines that the risk to the person from the investigational drug or investigational device is not greater than the risk from the disease or condition;

(3) the Secretary determines that an exemption for the investigational drug or investigational device is in effect under a regulation promulgated pursuant to section 505(i) or 520(g) and the sponsor of the drug or device and investigators comply with such regulation;

(4) the Secretary determines that the manufacturer of the investigational drug or investigational device is actively pursuing marketing approval with due diligence; and

(5) the Secretary determines that expanded access to the investigational drug or investigational device will not interfere with adequate enrollment of patients by the investigator in the ongoing clinical investigation of the investigational drug or investigational device authorized under section 505(i) or 520(g); and

(6) the Secretary determines that there is sufficient evidence of safety and effectiveness to support the expanded use of the investigational drug or investigational device in accordance with this section.

(b) PROTOCOLS.—A manufacturer or distributor may submit to the Secretary 1 or more expanded access protocols covering expanded access use of a drug or device described in subsection (a).

The protocols shall be subject to the provisions of section 505(i) or 520(g) and may include any form of use of the drug or device outside a clinical investigation, prior to approval of the drug or device for marketing including protocols for treatment use, emergency use, or uncontrolled trials, and single patient protocols. If the request for expanded access to an investigational drug or investigational device is intended for a single patient only, the Secretary may waive the requirements of paragraphs (3) and (4) of subsection (a) and accept a submission under sections 505(i) and 520(g) for an exemption for the investigational drug or investigational device for the single patient use. In the case of an emergency that does not allow sufficient time for a submission under section 505(i) or (520)(g), the Secretary may, prior to the submission, authorize the shipment of the investigational drug or investigational device for a single patient use.

(c) NOTIFICATION OF AVAILABILITY.—The Secretary shall inform national, State, and local medical associations and societies, voluntary health associations, and other appropriate persons about the availability of an investigational drug or investigational device under expanded access protocols submitted under this section, except that this subsection shall not apply to expanded access protocols for single patient use.

(d) TERMINATION.—The Secretary may at anytime terminate expanded access provided under subsection (a) for an investigational drug or investigational device if the requirements under this section are no longer met.

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SUBCHAPTER E—FAST TRACK DRUGS

SEC. 561. FAST TRACK DRUGS.

(a) DESIGNATION OF DRUG AS A FAST TRACK DRUG.—

(1) IN GENERAL.—The Secretary shall facilitate development, and expedite review and approval of new drugs and biological products that are intended for the treatment of serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs for such conditions. In this Act, such products shall be known as "Fast track drugs."

(2) REQUEST FOR DESIGNATION.—The sponsor of a drug (including a biological product) may request the Secretary to designate the drug as a fast track drug. A request for the designation may be made concurrently with, or at any time after, submission of an application for the investigation of the drug under section 505(i) or section 351(a)(4) of the Public Health Service Act.

(3) DESIGNATION.—Within 30 calendar days after the receipt of a request under paragraph (2), the Secretary shall determine whether the drug that is the subject of the request meets the criteria described in paragraph (1). If the Secretary finds that the drug meets the criteria, the Secretary shall designate the drug as a fast track drug and shall take such actions as are appropriate to expedite the development and review of the drug.

(b) APPROVAL OF APPLICATION FOR A FAST TRACK DRUG.—

(1) IN GENERAL.—The Secretary may approve an application for approval of a fast track drug under section 505(b) or section

351 of the Public Health Service Act (21 U.S.C. 262) upon a determination that the drug has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit.

(2) LIMITATION.—Approval of a fast track drug under this subsection may be subject to the requirements—

(A) that the sponsor conduct appropriate post-approval studies to validate the surrogate endpoint or otherwise confirm the clinical benefit of the drug; and

(B) that the sponsor submit copies of all promotional materials related to the fast track drug during the preapproval review period and following approval, at least 30 days prior to dissemination of the materials for such period of time as the Secretary deems appropriate.

(3) EXPEDITED WITHDRAWAL OF APPROVAL.—The Secretary may withdraw approval of a fast track drug using expedited procedures (as prescribed by the Secretary in regulations) including a procedure that provides an opportunity for an informal hearing, if—

(A) the sponsor fails to conduct any required post-approval study of the fast track drug with due diligence;

(B) a post-approval study of the fast track drug fails to verify clinical benefit of the fast track drug;

(C) other evidence demonstrates that the fast track drug is not safe or effective under conditions of use of the drug; or

(D) the sponsor disseminates false or misleading promotional materials with respect to the fast track drug.

(c) REVIEW OF INCOMPLETE APPLICATIONS FOR APPROVAL OF A FAST TRACK DRUG.—

(1) IN GENERAL.—If preliminary evaluation by the Secretary of clinical efficacy data for a fast track drug under investigation shows evidence of effectiveness, the Secretary shall evaluate for filing, and may commence review of portions, of an application for the approval of the drug if the applicant provides a schedule for submission of information necessary to make the application complete and any fee that may be required under section 736.

(2) EXCEPTION.—Any time period for review of human drug applications that has been agreed to by the Secretary and that has been set forth in goals identified in letters of the Secretary (relating to the use of fees collected under section 736 to expedite the drug development process and the review of human drug applications) shall not apply to an application submitted under paragraph (1) until the date on which the application is complete.

(d) AWARENESS EFFORTS.—The Secretary shall—

(1) develop and widely disseminate to physicians, patient organizations, pharmaceutical and biotechnology companies, and other appropriate persons a comprehensive description of the provisions applicable to fast track drugs established under this section; and

(2) establish an ongoing program to encourage the development of surrogate endpoints that are reasonably likely to pre-

dict clinical benefit for serious or life-threatening conditions for which there exist significant unmet medical needs.

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CHAPTER VII—GENERAL AUTHORITY

SUBCHAPTER A—GENERAL ADMINISTRATIVE PROVISIONS

REGULATIONS AND HEARINGS

SEC. 701 [371] [(a) The] *(a)(1) The* authority to promulgate regulations for the efficient enforcement of this Act, except as otherwise provided in this section, is hereby vested in the Secretary.

(2) Not later than February 27, 1999, the Secretary, after evaluating the effectiveness of the Good Guidance Practices document published in the Federal Register at 62 Fed. Reg. 8961, shall promulgate a regulation specifying the policies and procedures of the Food and Drug Administration for the development, issuance, and use of guidance documents.

* * * * * * *

PRESUMPTION

SEC. 709. In any action to enforce the requirements of this Act respecting [a device] *a device, food, drug, or cosmetic.* The connection with interstate commerce required for jurisdiction in such action shall be presumed to exist.

PART 2—FEES RELATING TO DRUGS

SEC. 735. DEFINITIONS.

For purposes of this subchapter:

(1) The term "human drug application" means an application for—

* * * * * * *

Such term does not include a supplement to such an application, does not include an application with respect to whole blood or a blood component for transfusion, does not include an application with respect to a bovine blood product for topical application licensed before September 1, 1992, an allergenic extract product, or an in vitro diagnostic biologic product licensed under section 351 of the Public Health [Service Act, and] *Service Act,* does not include an application with respect to a large volume parenteral drug product approved before [September 1, 1992.] *September 1, 1992, does not include an application for a licensure of a biological product for further manufacturing use only, and does not include an application or supplement submitted by a State or Federal Government entity for a drug or biological product that is not distributed commercially. Such term does include an application for licensure, as described in subparagraph (D), of a large volume biological product intended for single dose injection for intravenous use or infusion.*

* * * * * * *

Such term does not include whole blood or a blood component for transfusion, does not include a bovine blood product for topical application licensed before September 1, 1992, an allergenic extract product, or an in vitro diagnostic biologic product licensed under section 351 of the Public Health [Service Act, and] *Service Act,* does not include a large volume parenteral drug product approved before [September 1, 1992.] *September 1, 1992, does not include biological product that is licensed for further manufacturing use only, and does not include a drug or biological product that is not distributed commercially and is the subject of an application or supplement submitted by a State or Federal Government entity. Such term does include a large volume biological product intended for single dose injection for intravenous use or infusion.*

(4) The term "final dosage form" means, with respect to a prescription drug product, a finished dosage form which is approved for administration to a patient [without] *without substantial* further manufacturing.

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(7) The term "costs of resources allocated for the process for the review of human drug applications" means the expenses incurred in connection with the process for the review of human drug applications for—

(A) officers and employees of the Food and Drug Administration, [employees under contract with the Food and Drug Administration who work in facilities owned or leased for the Food and Drug Administration,] *Contractors of the Food and Drug Administration* advisory committees, and costs related to such officers, employees, [and committees,] *and committees and to contracts with such contractors,*

* * * * * * *

(8) The term "adjustment factor" applicable to a fiscal year is the lower of—

(A) the Consumer Price Index for all urban consumers (all items; United States city average) for [August of] *April of* the preceding fiscal year divided by such Index for [August 1992] *April 1997*, or

[(B) the total of discretionary budget authority provided for programs in the domestic category for the immediately preceding fiscal year (as reported in the Office of Management and Budget sequestration preview report, if available, required under section 254(d) of the Balanced Budget and Emergency Deficit Control Act of 1985) divided by such budget authority for fiscal year 1992 (as reported in the Office of Management and Budget final sequentration report submitted after the end of the 102d Congress, 2d Session).]

(B) 1 plus the total percentage increase for such fiscal year since fiscal year 1997 in basic pay under the General Schedule in accordance with section 5332 of title 5, United States Code, as adjusted by any locality-based comparabil-

ity payment pursuant to section 5304 of such title for Federal employees stationed in the District of Columbia.

[The terms "budget authority" and "category" in subparagraph (B) are as defined the Balanced Budget and Emergency Deficit Control Act of 1985, as in effect as of September 1, 1992.]

(9) The term affiliate means a business entity that has a relationship with a second business entity if, directly or indirectly—

(A) 1 business entity controls, or has the power to control, the other business entity; or

(B) a third party controls, or has power to control both of the business entities.

* * * * * * *

SEC. 736. AUTHORITY TO ASSESS AND USE DRUG FEES.

(a) TYPE OF FEES.—[Beginning in fiscal year 1993] *Beginning in fiscal year 1988*, the Secretary shall assess and collect fees in accordance with this section as follows:

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(B) PAYMENT SCHEDULE.—

[(i) FIRST PAYMENT.—50 percent of the fee required by subparagraph (A) shall be due upon submission of the application or supplement.

[(ii) FINAL PAYMENT.—The remaining 50 percent of the fee required by subparagraph (A) will be due upon—

[(I) the expiration of 30 days from the date the Secretary sends to the applicant a letter designated by the Secretary as an action letter described in section 735(6)(B), or

[(II) the withdrawal of the application or supplement after it is filed unless the Secretary waives the fee or a portion of the fee because no substantial work was performed on such application or supplement after it was filed.

The designation under subclause (I) or the waiver under subclause (II) shall be solely in the discretion of the Secretary and shall not be reviewable.]

(B) PAYMENT.—The fee required by subparagraph (A) shall be due upon submission of the application or supplement.

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(D) REFUND OF FEE IF APPLICATION [NOT ACCEPTED] *REFUSED* for filing.—THE SECRETARY SHALL REFUND [50 PERCENT] *75 percent* of the fee paid under [subparagraph (B)(i)] *subparagraph (B)* for any application or supplement which is [not accepted] *refused* for filing.

(E) EXCEPTION FOR DESIGNATED ORPHAN DRUG OR INDICATION.—A person that submits a human drug application for a prescription drug product that has been designated as a drug for a rare disease or condition pursuant to section 526, or a supplement proposing to include a new indication for a rare disease or condition pursuant to section 526, shall not be assessed a fee under subparagraph (A), unless

the human drug application includes indications for other than rare diseases or conditions.

(F) EXCEPTION FOR APPLICATIONS AND SUPPLEMENTS FOR PEDIATRIC INDICATIONS.—A person that submits a human drug application or supplement that includes an indication for use in pediatric populations shall be assessed a fee under subparagraph (A) only if—

(i) the application is for initial approval for use in a pediatric population; or

(ii) the application or supplement is for approval for use in pediatric and nonpediatric populations.

(G) REFUND OF FEE IF APPLICATION WITHDRAWN.—If an application or supplement is withdrawn after the application or supplement is filed, the Secretary may waive and refund the fee or a portion of the fee if no substantial work was performed on the application or supplement after the application or supplement was filed. The Secretary shall have the sole discretion to waive and refund a fee or a portion of the fee under this subparagraph. A determination by the Secretary concerning a waiver or refund under this paragraph shall not be reviewable.

(2) PRESCRIPTION DRUG ESTABLISHMENT FEE.—Each person that—

(A) owns a prescription drug establishment, at which is manufactured at least 1 prescription drug product which is not the, or not the same as a, product approved under an application filed under section 505(b)(2) or [505(j), and] *505(j) or under an abbreviated new drug application pursuant to regulations in effect prior to the implementation of the Drug Price Competition and Patent Term Restoration Act of 1984, or a product approved under an application filed under section 507 that is abbreviated, and*

* * * * * * *

(3) PRESCRIPTION DRUG PRODUCT FEE.—

(A) IN GENERAL.—Except as provided in subparagraph (B), each person—

(i) who is named as the applicant in a human drug application for a prescription drug product which [is listed] *has been submitted for listing* under section 510, and

(ii) who, after September 1, 1992, had pending before the Secretary a human drug application or supplement,

shall pay for each such prescription drug product the annual fee established in subsection (b). [Such fee shall be payable at the time of the first such listing of such product in each calendar year. Such fee shall be paid only once each year for each listed prescription drug product irrespective of the number of times such product is listed under section 510.] *Such fee shall be payable for the fiscal year in which the product is first submitted for listing under section 510, or for relisting under section 510 if the product has been withdrawn from listing and relisted. After such fee is paid for that fiscal year, such fee shall be*

payable on or before January 31 of each year. Such fee shall be paid only once for each product for a fiscal year in which the fee is payable.

(B) EXCEPTION.—The listing of a prescription drug product under section 510 shall not require the person who listed such product to pay the fee prescribed by subparagraph (A) if such product is the same product as a product approved under an application filed under section 505(b)(2) or [505(j).] *505(j), or under an abbreviated new drug application pursuant to regulations in effect prior to the implementation of the Drug Price Competition and Patent Term Restoration Act of 1984, or is a product approved under an application filed under section 507 that is abbreviated.*

[(b) FEE AMOUNTS.—]

(b) FEE AMOUNTS.—Except as provided in subsections (c), (d), (f), and (g), the fees required under subsection (a) shall be determined and assessed as follows:

(1) APPLICATION AND SUPPLEMENT FEES.—

(A) FULL FEES.—The application fee under subsection (a)(1)(A)(i) shall be $250,704 in fiscal year 1998, $256,338 in each of fiscal years 1999 and 2000, $267,606 in fiscal year 2001, and $258,451 in fiscal year 2002.

(B) OTHER FEES.—The fee under subsection (a)(1)(A)(ii) shall be $125,352 in fiscal year 1998, $128,169 in each of fiscal years 1999 and 2000, $133,803 in fiscal year 2001 and $129,226 in fiscal year 2002.

(2) FEE REVENUES FOR ESTABLISHMENT FEES.—The total fee revenues to be collected in establishment fees under subsection (a)(2) shall be $35,600,000 in fiscal year 1998, $36,400,000 in each of fiscal years 1999 and 2000, $38,000,000 in fiscal year 2001, and $36,700,000 in fiscal year 2002.

(3) TOTAL FEE REVENUES FOR PRODUCT FEES.—The total fee revenues to be collected in product fees under subsection (a)(3) in a fiscal year shall be equal to the total fee revenues collected in establishment fees under subsection (a)(2) in that fiscal year.

* * * * * * *

(c) [INCREASES AND] ADJUSTMENTS.—

[(1) REVENUE INCREASE.—The total fee revenues established by the schedule in subsection (b)(1) shall be increased by the Secretary] *(1) Inflation adjustment.—The fees and total fee revenues established in subsection (b) shall be adjusted by the Secretary* by notice, published in the Federal Register, for a fiscal year to reflect the greater of—

(A) the total percentage [increase] *change* that occurred during the preceding fiscal year in the Consumer Price Index for all urban consumers (all items; U.S. city average), or

(B) the total percentage [increase] *change* for such fiscal year in basic pay under the General Schedule in accordance with section 5332 of title 5, United States Code, as adjusted by any locality-based comparability payment pursuant to section 5304 of such title for Federal employees stationed in the District of Columbia.

The adjustment made each fiscal year by this subsection will be added on a compounded basis to the sum of all adjustments made each fiscal year after fiscal year 1997 under this subsection.

(2) ANNUAL FEE ADJUSTMENT.—Subject to the amount appropriated for a fiscal year under subsection (g), the Secretary shall, within 60 days after the end of each fiscal year beginning after [October 1, 1992, adjust the fees established by the schedule in subsection (b)(1) for the following fiscal year to achieve the total fee revenues, as may be increased under paragraph (1). Such fees shall be adjusted under this paragraph to maintain the proportions established in such schedule.] *September 30, 1997, adjust the establishment and product fees described in subsection (b) for the fiscal year in which the adjustment occurs so that the revenues collected from each of the categories of fees described in paragraphs (2) and (3) of subsection (b) shall be set to be equal to the revenues collected during the past fiscal year from the category of application and supplement fees described in paragraph (1) of subsection (b).*

(3) LIMIT.—The total amount of fees charged, as adjusted under [paragraph (2)] *this subsection*, for a fiscal year may not exceed the total costs for such fiscal year for the resources allocated for the process for review of human drug applications.

(d) FEE WAIVER OR REDUCTION.—[The Secretary shall grant a waiver from or a reduction of 1 or more fees under subsection (a) where the Secretary finds that—] *(1) IN GENERAL.—The Secretary shall grant a waiver from or a reduction of 1 or more fees assessed under subsection (a) where the Secretary finds that—*

[(1)] *(A)* such waiver or reduction is necessary to protect the public health,

[(2)] *(B)* the assessment of the fee would present a significant barrier to innovation because of limited resources available to such person or other circumstances,

[(3)] *(C)* the fees to be paid by such person will exceed the anticipated present and future costs incurred by the Secretary in conducting the process for the review of human drug applications for such person[, or],

[(4)] *(D)* assessment of the fee for an application or a supplement filed under section 505(b)(1) pertaining to a drug containing an active ingredient would be inequitable because an application for a product containing the same active ingredient filed by another person under section 505(b)(2) could not be assessed fees under subsection (a)(1)[.], *or;*

(E) the applicant is a small business submitting its first human drug applicaiton to the Secretary for review.

[In making the finding in paragraph (3), the Secretary may use standard costs.]

(2) USE OF STANDARD COSTS.—In making the finding in paragraph (1)(C), the Secretary may use standard costs.

(3) RULES RELATING TO SMALL BUSINESSES.—

(A) DEFINITION.—In paragraph (1)(E), the term "small business" means an entity that has fewer than 500 employees, including employees of affiliates.

(B) WAIVER OF APPLICATION FEE.—The Secretary shall waive under paragraph (1)(E) the application fee for the first human drug application that a small business or its affiliate submits to the Secretary for review. After a small business or its affiliate is granted such a waiver, the small business or its affiliate shall pay—

(i) application fees for all subsequent human drug applications submitted to the Secretary for review in the same manner as an entity that does not qualify as a small business; and

(ii) all supplement fees for all supplements to human drug applications submitted to the Secretary for review in the same manner as an entity that does not qualify as a small business.

* * * * * * *

(f) ASSESSMENT OF FEES.—

(1) LIMITATION.—Fees may not be assessed under subsection (a) for a fiscal year beginning after [fiscal year 1993] *fiscal year 1997* unless appropriations for salaries and expenses of the Food and Drug Administration for such fiscal year (excluding the amount of fees appropriated for such fiscal year) are equal to or greater than the amount of appropriations for the salaries and expenses of the Food and Drug Administration for the [fiscal year 1992] *fiscal year 1997 (excluding the amount of fees appropriated for such fiscal year)* multiplied by the adjustment factor applicable to the fiscal year involved.

* * * * * * *

(g) CREDITING AND AVAILABILITY OF FEES.—

(1) IN GENERAL.—Fees collected for a fiscal year pursuant to subsection (a) shall be credited to the appropriation account for salaries and expenses of the Food and Drug Administration and shall be available in accordance with appropriation Acts until expended without fiscal year limitation. *Such sums as may be necessary may be transferred from the Food and Drug Administration salaries and expenses appropriation account without fiscal year limitation to such appropriation account for salaries and expenses with such fiscal year limitation. The sums transferred shall be available solely for the process for the review of human drug applications within the meaning of section 735(6).*

(2) COLLECTIONS AND APPROPRIATION ACTS.—The fees authorized by this section—

(A) shall be collected in each fiscal year in an amount equal to the amount specified in appropriation [Acts] *Acts, or otherwise made available for obligation* for such fiscal year, and

(B) shall only be collected and available to defray increases in the costs of the resources allocated for the process for the review of human drug applications (including increases in such costs for an additional number of full-time equivalent positions in the Department of Health and Human Services to be engaged in such process) [over such costs for fiscal year 1992] *over such costs, excluding costs*

paid from fees collected under this section, for fiscal year 1997 multiplied by the adjustment factor.

[(3) AUTHORIZATION OF APPROPRIATIONS.—There are authorized to be appropriated for fees under this section—

[(A) $36,000,000 for fiscal year 1993,

[(B) $54,000,000 for fiscal year 1994,

[(C) $75,000,000 for fiscal year 1995,

[(D) $78,000,000 for fiscal year 1996, and

[(E) $84,000,000 for fiscal year 1997, as adjusted to reflect increases in the total fee revenues made under subsection (c)(1).]

(3) AUTHORIZATION OF APPROPRIATIONS.—There is authorized to be appropriated for fees under this section—

(A) $106,800,000 for fiscal year 1998;

(B) $109,200,000 for fiscal year 1999;

(C) $109,200,000 for fiscal year 2000;

(D) $114,000,000 for fiscal year 2001; and

(E) $110,100,000 for fiscal year 2002,

as adjusted to reflect adjustments in the total fee revenues made under this section and changes in the total amounts collected by application, supplement, establishment, and product fees.

(4) OFFSET.—Any amount of fees collected for a fiscal year which exceeds the amount of fees specified in appropriation Acts for such fiscal year, shall be credited to the appropriation account of the Food and Drug Administration as provided in paragraph (1), and shall be subtracted from the amount of fees that would otherwise be authorized to be collected under appropriation Acts for a subsequent fiscal year.

* * * * * * *

(i) WRITTEN REQUESTS FOR WAIVERS, REDUCTIONS, AND REFUNDS.—To qualify for consideration for a waiver or reduction under subsection (d), or for a refund, of any fee collected in accordance with subsection (a), a person shall submit to the Secretary a written request for such waiver, reduction, or refund not later than 180 days after such fee is due.

[(i)] *(j)* CONSTRUCTION.—This section may not be construed to require that the number of full-time equivalent position in the Department of Health and Human Services, for officers, employers, and advisory committees not engaged in the process of the review of human drug applications, be reduced to offset the number of officers, employees, and advisory committees so engaged.

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SUBCHAPTER D—CLASSIFICATION OF PRODUCT AND ENVIRONMENTAL IMPACT REVIEWS

SEC. 741. CLASSIFICATION OF PRODUCTS.

(a) REQUEST.—A person who submits an application or submission (including a petition, notification, and any other similar form of request) under this Act, may submit a request to the Secretary respecting the classification of an article (including an article that is a combination product subject to section 503(g)) as a drug, biological product, or device, or respecting the component of the Food and

Drug Administration that will regulate the article. In submitting the request, the person shall recommend a classification for the article, or a component to regulate the article, as appropriate.

(b) STATEMENT.—Not later than 60 days after the receipt of the request described in subsection (a), the Secretary shall determine the classification of the article or the component of the Food and Drug Administration that will regulate the article and shall provide to the person a written statement that identifies the classification of the article or the component of the Food and Drug Administration that will regulate the article and the reasons for such determination. The Secretary may not modify such statement except with the written consent of the person or for public health reasons.

(c) INACTION OF SECRETARY.—If the Secretary does not provide the statement within the 60-day period described in subsection (b), the recommendation made by the person under subsection (a) shall be considered to be a final determination by the Secretary of the classification of the article or the component of the Food and Drug Administration that will regulate the article and may not be modified by the Secretary except with the written consent of the person or for public health reasons.

* * * * * * *

SEC. 742. ENVIRONMENTAL IMPACT REVIEW.

Nothwithstanding any other provision of law, no action by the Secretary pursuant to this Act shall be subject to an environmental assessment, an environmental impact statement, or other environmental consideration unless the Secretary demonstrates, in writing—

(1) that there is a reasonable probability that the environmental impact of the action is sufficiently substantial and within the factors that the Secretary is authorized to consider under this Act; and

(2) that consideration of the environmental impact will directly affect the decision on the action.

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SUBCHAPTER E—MANUFACTURING CHANGES

SEC. 751. MANUFACTURING CHANGES.

(a) IN GENERAL.—A change in the manufacture of a new drug, including a biological product, may be made in accordance with this section.

(b) CHANGES.—

(1) VALIDATION.—Before distributing a drug made after a change in the manufacture of the drug from the manufacturing process established in the approved new drug application under section 505, or license application under section 351 of the Public Health Service Act, the applicant shall validate the effect of the change on the identity, strength, quality, purity, and potency of the drug as the identity, strength, quality, purity, and potency may relate to the safety or effectiveness of the drug.

(2) REPORTS.—The applicant shall report the change described in paragraph (1) to the Secretary and may distribute a drug made after the change as follows:

(A) MAJOR MANUFACTURING CHANGES.

(i) IN GENERAL.—Major manufacturing changes, which are of a type determined by the Secretary to have substantial potential to adversely affect the identity, strength, quality, purity, or potency of the drug as the identity, strength, quality, purity, and potency may relate to the safety or effectiveness of a drug, shall be submitted to the Secretary in a supplemental application and drugs made after such changes may not be distributed until the Secretary approves the supplemental application.

(ii) DEFINITION.—In this subparagraph, the term "major manufacturing changes" means—

(I) changes in the qualitative or quantitative formulation of a drug or the specifications in the approved marketing application for the drug (unless exempted by the Secretary from the requirements of this subparagraph);

(II) changes that the Secretary determines by regulation or issuance of guidance require completion of an appropriate human study demonstrating equivalence of the drug to the drug manufactured before such changes; and

(III) other changes that the Secretary determines by regulation or issuance of guidance have a substantial potential to adversely affect the safety or effectiveness of the drug.

(B) OTHER MANUFACTURING CHANGES.—

(i) IN GENERAL.—As determined by the Secretary, manufacturing changes other than major manufacturing changes shall—

(I) be made at any time and reported annually to the Secretary, with supporting data; or

(II) be reported to the Secretary in a supplemental application.

(ii) DISTRICTION OF THE DRUG.—In the case of changes reported in accordance with clause (i)(II)—

(I) the applicant may distribute the drug 30 days after the Secretary receives the supplemental application unless the Secretary notifies the applicant within such 30-day period that prior approval of such supplemental application is required; and

(II) the Secretary shall, after making the notification to the applicant under subclause (I), approve or disapprove each such supplemental application.

(iii) SPECIAL RULE.—The Secretary may determine types of manufacturing changes after which distribution of a drug may commence at the time of submission of supplemental application.

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SUBCHAPTER F—NATIONAL UNIFORMITY FOR NONPRESCRIPTION DRUGS FOR HUMAN USE AND COSMETICS

SEC. 761. NATIONAL UNIFORMITY FOR NONPRESCRIPTION DRUGS AND COSMETICS.

(a) IN GENERAL.—Except as provided in subsection (b), (c)(1), or (d), no State or political subdivision of a State may establish or continue in effect any requirement—

(1) that relates to the regulation of a drug intended for human use that is not subject to the requirements of section 503(b)(1) or a cosmetic; and

(2) that is different from or in addition to, or that is otherwise not identical with, a requirement of this Act, the Poison Prevention Packaging Act of 1970 (15 U.S.C. 1471 et seq.), or the Fair Packaging and Labeling Act (15 U.S.C. 1451 et seq.).

(b) EXEMPTION.—Upon application of a State, the Secretary may by regulation, after notice and opportunity for written and oral presentation of views, exempt from subsection (a), under such condition as may be prescribed in such regulation a State requirement that——

(1) protects an important public interest that would otherwise be unprotected.

(2) would not cause any drug or cosmetic to be in violation of any applicable requirement or prohibition under Federal law; and

(3) would not unduly burden interstate commerce.

(c) SCOPE.—For purposes of subsection (a), a requirement that relates to the regulation of a drug or cometic—

(1) shall not include any requirement that relates to the practice of pharmacy or any requirement that a drug be dispensed only upon the prescription of a practitioner licensed by law to administer such drug; and

(2) shall be deemed to include any requirement relating to public information or any other form of public communication relating to the safety or effectiveness of a drug or cosmetic.

(d) NO EFFECT ON PRODUCT LIABILITY LAW.—Nothing in this section shall be construed to modify or otherwise affect any action or the liability of any person under the product liability law of any State.

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SEC. 903. [393] FOOD AND DRUG ADMINISTRATION.

(a) IN GENERAL.—* * *

* * * * * * *

(b) MISSION.—

(1) IN GENERAL.—The Administration shall protect the public health by ensuring that—

(A) foods are safe, wholesome, sanitary, and properly labeled;

(B) human and veterinary drugs are safe and effective;

(C) there is reasonable assurance of safety and effectiveness of devices intended for human use;

(D) cosmetics are safe; and

(E) public health and safety are protected from electronic product radiation.

(2) SPECIAL RULES.—The Administration shall promptly and efficiently review clinical research and take appropriate action on the marketing of regulated products in a manner that does not unduly impede innovation or product availability. The Administration shall participate with other countries to reduce the burden of regulation, to harmonize regulatory requirements, and to achieve appropriate reciprocal arrangements with other countries.

(3) INTERAGENCY COLLABORATION.—The Secretary shall implement programs and policies that will foster collaboration between the Administration, the National Institutes of Health, and other science-based Federal agencies, to enhance the scientific and technical expertise available to the Secretary in the conduct of the duties of the Secretary with respect to the development, clinical investigation, evaluation, and postmarket monitoring of emerging medical therapies, including complementary therapies, and advances in nutrition and food science.

(4) AGENCY PLAN FOR STATUTORY COMPLIANCE.—

(A) IN GENERAL.—Not later than 180 days after the date of enactment of this paragraph, the Secretary, after consultation with relevant experts, health care professionals, representatives of patient and consumer advocacy groups, and the regulated industry, shall develop and publish in the Federal Register a plan bringing the Secretary into compliance with each of the obligations of the Secretary under this Act and other relevant statutes. The Secretary shall biannually review the plan and shall revise the plan as necessary, in consultation with such persons.

(B) OBJECTIVES OF AGENCY PLAN.—The plan required by subparagraph (A) shall establish objectives, and mechanisms to be used by the Secretary, acting through the Commissioner, including objectives and mechanisms that—

(i) minimize deaths of, and harm to, persons who use or may use an article regulated under this Act;

(ii) maximize the clarity of, and the availability of information about, the process for review of applications and submissions (including petitions, notifications, and any other similar forms of request) made under this Act, including information for potential consumers and patients concerning new products;

(iii) implement all inspection and postmarket monitoring provisions of this Act by July 1, 1999;

(iv) ensure access to the scientific and technical expertise necessary to ensure compliance by the Secretary with the statutory obligations described in subparagraph (A);

(v) establish a schedule to bring the Administration into full compliance by July 1, 1999, with the time periods specified in this Act for the review of all applications and submissions described in clause (ii) and submitted after the date of enactment of this paragraph; and

(vi) reduce backlogs in the review of all applications and submissions described in clause (ii) for any article with the objective of eliminating all backlogs in the review of the applications and submissions by January 1, 2000.

(5) ANNUAL REPORT.—

(A) CONTENTS.—The Secretary shall prepare and publish in the Federal Register and solicit public comment on an annual report that—

(i) provides detailed statistical information on the performance of the Secretary under the plan described in paragraph (4);

(ii) compares such performance of the Secretary with the objectives of the plan and with the statutory obligations of the Secretary;

(iii) analyzes any failure of the Secretary to achieve any objective of the plan or to meet any statutory obligation;

(iv) identifies any regulatory policy that has a significant impact on compliance with any objective of the plan or any statutory obligation; and

(v) sets forth any proposed revision to any such regulatory policy, or objective of the plan that has not been met.

(B) STATISTICAL INFORMATION.—The statistical information described in subparagraph (A)(i) shall include a full statistical presentation relating to all applications and submissions (including petitions, notifications, and any other similar forms of request) made under this Act and approved or subject to final action by the Secretary during the year covered by the report. In preparing the statistical presentation, the Secretary shall take into account the date of—

(i) the submission of any investigational application;

(ii) the application of any clinical hold;

(iii) the submission of any application or submission (including a petition, notification, and any other similar form of request) made under this Act for approval or clearance;

(iv) the acceptance for filing of any application or submission described in clause (iii) for approval or clearance;

(v) the occurrence of any anapprovable action;

(vi) the occurrence of any approvable action; and

(vii) the approval or clearance of any application or submission described in clause (iii).

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[(b)**]** *(c)* COMMISSIONER.—

(1) APPOINTMENT.—* * *

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[(c)**]** *(d)* TECHNICAL AND SCIENTIFIC REVIEW GROUPS.—The Secretary through the Commissioner of Food and Drugs may, without regard to the provisions of title 5, United States Code, governing appointments in the competitive service and without regard to the

provisions of chapter 51 and subchapter III of chapter 53 of such title relating to classification and General Schedule pay rates, establish such technical and scientific review groups as are needed to carry out the functions of the Administration, including functions under the Federal Food, Drug, and Cosmetic Act, and appoint and pay the members of such groups, except that officers and employees of the United States shall not receive additional compensation for service as members of such groups.

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SEC. 906. CONTRACTS FOR EXPERT REVIEW.

(a) IN GENERAL.—

(1) AUTHORITY.—The Secretary may enter into a contract with any organization or any individual (who is not an employee of the Department) with expertise in a relevant discipline, to review, evaluate, and make recommendations to the Secretary on part or all of any application or submission (including a petition, notification, and any other similar form of request) made under this Act for the approval or classification of an article or made under section 351(a) of the Public Health Service Act (42 U.S.C. 262(a)) with respect to a biological product. Any such contract shall be subject to the requirements of section 708 relating to the confidentiality of information.

(2) INCREASED EFFICIENCY AND EXPERTISE THROUGH CONTRACTS.—The Secretary shall use the authority granted in paragraph (1) whenever the Secretary determines that a contract described in paragraph (1) will improve the timeliness or quality of the review of an application or submission described in paragraph (1). Such improvement may include providing the Secretary increased scientific or technical expertise that is necessary to review or evaluate new therapies and technologies.

(b) REVIEW OF EXPERT REVIEW.—

(1) IN GENERAL.—Subject to paragraph (2), the official of the Food and Drug Administration responsible for any matter for which expert review is used pursuant to subsection (a) shall review the recommendations of the organization or individual who conducted the expert review and shall make a final decision regarding the matter within 60 days after receiving the recommendations.

(2) LIMITATION.—A final decision under paragraph (1) shall be made within the applicable prescribed time period for review of the matter as set forth in this Act or in the Public Health Service Act (42 U.S.C. 201 et seq.).

(3) AUTHORITY OF SECRETARY.—Notwithstanding subsection (a), the Secretary shall retain full authority to make determinations with respect to the approval or disapproval of an article under this Act, the approval or disapproval of a biologics license with respect to a biological product under section 351(a) of the Public Health Service Act, or the classification of an article as a device under section 513(f)(1).

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SEC. 907. INTRAMURAL RESEARCH TRAINING AWARD PROGRAM.

(a) IN GENERAL.—The Secretary, acting through the Commissioner of Food and Drugs, may, directly or through grants, contracts, or cooperative agreements, conduct and support intramural research training in regulatory scientific programs by predoctoral and postdoctoral scientists and physicians, including the support through the use of fellowships.

(b) LIMITATION ON PARTICIPATION.—A recipient of a fellowship under subsection (a) may not be an employee of the Federal Government.

(c) SPECIAL RULE.—The Secretary, acting through the Commissioner of Food and Drugs, may support the provision of assistance for fellowships described in subsection (a) through a Cooperative Research and Development Agreement.

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PUBLIC HEALTH SERVICE ACT

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PART F—LICENSING—BIOLOGICAL PRODUCTS AND CLINICAL LABORATORIES

Subpart 1—Biological Products

REGULATION OF BIOLOGICAL PRODUCTS

SEC. 351. [262] [(a) No person shall sell, barter, or exchange, or offer for sale, barter, or exchange in the District of Columbia, or send, carry, or bring for sale, barter, or exchange from any State or possession into any other State or possession or into any foreign country, or from any foreign country into any State or possession, any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or its derivatives (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of diseases or injuries of man, unless (1) such virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or other product has been propagated or manufactured and prepared at an establishment holding an unsuspended and unrevoked license, issued by the Secretary as hereinafter authorized, to propagate or manufacture, and prepare such virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or other product for sale in the District of Columbia, or for sending, bringing, or carrying from place to place aforesaid: and (2) each package of such virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or other product is plainly marked with the proper name of the article contained therein, the name, address, and license number of the manufacturer, and the date beyond which the contents cannot be expected beyond reasonable doubt to yield their specific results. The suspension or revocation of any license shall not prevent the sale, barter, or exchange of any virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or other product aforesaid which has been sold and delivered by the

licensee prior to such suspension or revocation, unless the owner or custodian of such virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or other product aforesaid has been notified by the Secretary not to sell, barter, or exchange the same.] *(a)(1) Except as provided in paragraph (4), no person shall introduce or deliver for introduction into interstate commerce any biological product unless—*

(A) a biologics license is in effect for the biological product; and

(B) each package of the biological product is plainly marked with—

(i) the proper name of the biological product contained in the package;

(ii) the name, address, and applicable license number of the manufacturer of the biological product; and

(iii) the expiration date of the biological product.

(2)(A) The Secretary shall establish, by regulation, requirements for the approval, suspension, and revocation of biologics licenses.

(B) The Secretary shall approve a biologics license application on the basis of a demonstration that—

(i) the biological product that is the subject of the application is safe, pure, and potent; and

(ii) the facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent.

(3) A biologics license application shall be approved only if the applicant (or other appropriate person) consents to the inspection of the facility that is the subject of the application, in accordance with subsection (c).

(4) The Secretary shall prescribe requirements under which a biological product undergoing investigation shall be exempt from the requirements of paragraph (1).

[(b) No person shall falsely label or mark any package or container or any virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or other product aforesaid; nor alter any label or mark on any package or container of any virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or other product aforesaid so as to falsify such label or mark.]

(b) No person shall falsely label or mark any package or container of any biological product or alter any label or mark on the package or container of the biological product so as to falsify the label or mark.

(c) Any officer, agent, or employee of the Department of Health and Human Services, authorized by the Secretary for the purpose, may during all reasonable hours enter and inspect any establishment for the propagation or manufacture and preparation of any [virus, serum, toxin, antitoxin, vaccine, blood, blood component or other product aforesaid for sale barter, or exchange in the District of Columbia, or to be sent, carried, or brought from any State or possession into any other State or possession or into any foreign country, or from any foreign country into any State or possession.] *biological product.*

[(d)(1) Licenses for the maintenance of establishments for the propagation or manufacture and preparation of products described in subsection (a) of this section may be issued only upon a showing that the establishment and the products for which a license is desired meet standards, designed to insure the continued safety, purity, and potency of such products, prescribed in regulations, and licenses for new products may be issued only upon a showing that they meet such standards. All such licenses shall be issued, suspended, and revoked as prescribed by regulations and all licenses issued for the maintenance of establishment for the propagation or manufacture and preparation, in any foreign country, of any such products for sale, barter, or exchange in any State or possession shall be issued upon condition that the licensees will permit the inspection of their establishment in accordance with subsection (c) of this section.]

[(2)(A) Upon] *(d)(1) Upon* a determination that a batch, lot, or other quantity of a product licensed under this section presents an imminent or substantial hazard to the public health, the Secretary shall issue an order immediately ordering the recall of such batch, lot, or other quantity of such product. An order under this paragraph shall be issued in accordance with section 554 of title 5, United States Code.

[(B)] *(2)* Any violation of [subparagraph (A)] *paragraph (1)* shall subject the violator to a civil penalty of up to $100,000 per day of violation. The amount of a civil penalty under [this subparagraph] *this paragraph* shall, effective December 1 of each year beginning 1 year after the effective date of [this subparagraph] *this paragraph*, be increased by the percent change in the Consumer Price Index for the base quarter of such year over the Consumer Price Index for the base quarter of the preceding year, adjusted to the nearest 1/10 of 1 percent. For purposes of [this subparagraph] *this paragraph*, the term "base quarter", as used with respect to a year, means the calendar quarter ending on September 30 of such year and the price index for a base quarter is the arithmetical mean of such index for the 3 months comprising such quarter.

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(i) In this section, the term 'biological product' means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

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TITLE IV—NATIONAL RESEARCH INSTITUTES

PART A—NATIONAL INSTITUTES OF HEALTH

ORGANIZATION OF THE NATIONAL INSTITUTES OF HEALTH

SEC. 401. (a) * * *

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APPOINTMENT AND AUTHORITY OF DIRECTOR OF NIH

SEC. 402. (a) * * *

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(j)(1) The Secretary, acting through the Director of the National Institutes of Health and subject to the availability of appropriations, shall establish, maintain, and operate a program with respect to information on research relating to the treatment, detection, and prevention of serious or life-threatening diseases and conditions. The program shall, with respect to the agencies of the Department of Health and Human Services, be integrated and coordinated, and, to the extent practicable, coordinated with other data banks containing similar information.

(2)(A) After consultation with the Commissioner of Food and Drugs, the directors of the appropriate agencies of the National Institutes of Health (including the National Library of Medicine), and the Director of the Centers for Disease Control and Prevention, the Secretary shall, in carrying out paragraph (1), establish a data bank of information on clinical trials for drugs, and biologicals, for serious or life-threatening diseases and conditions.

(B) In carrying out subparagraph (A), the Secretary shall collect, catalog, store and disseminate the information described in such subparagraph. The Secretary shall disseminate such information through information systems, which shall include toll-free telephone communications, available to individuals with serious or life-threatening diseases and conditions, to other members of the public, to health care providers, and to researchers.

(3) The Data Bank shall include the following:

(A) A registry of clinical trials (whether federally or privately funded) of experimental treatments for serious or life-threatening diseases and conditions under regulations promulgated pursuant to sections 505 and 520 of the Federal Food, Drug, and Cosmetic Act that provides a description of the purpose of each experimental drug or biological protocol, either with the consent of the protocol sponsor, or when a trial to test efficacy begins. Information provided shall consist of eligibility criteria, a description of the location of trial sites, and a point of contact for those wanting to enroll in the trial, and shall be in a form that can be readily understood by embers of the public. Such information must be forwarded to the Data Bank by the sponsor of the trial not later than 21 days after the approval by the Food and Drug Administration.

(B) Information pertaining to experimental treatments for serious or life-threatening diseases and conditions that may be available—

(i) under a treatment investigational new drug application that has been submitted to the Food and Drug Administration pursuant to part 312 of title 21, Code of Federal Regulations; or

(ii) as a Group C cancer drug.

The Data Bank may also include information pertaining to the results of clinical trials of such treatments, with the consent of the sponsor, including information concerning potential

toxicities or adverse effects associated with the use or administration of such experimental treatments.

(4) The Data Bank shall not include information relating to an investigation if the sponsor has certified to the Secretary that disclosure of such information would substantially interfere with the timely enrollment of subjects in the investigation.

(5) For the purpose of carrying out this subsection, there are authorized to be appropriated such sums as may be necessary. Fees collected under section 736 of the Federal Food, Drug, and Cosmetic (21 U.S. C. 379h) shall not be authorized or appropriated for use in carrying out this subsection.

[(j)**]** *(k)*(1) The Director of NIH may establish a program to provide day care services for the employees of the National Institutes of Health similar to those services provided by other Federal agencies (including the availability of day care service on a 24-hour-a-day basis).

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[(k)**]** *(l)* The Director of NIH shall carry out the program established in part F of title XII (relating to interagency research on trauma).

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CONTROLLED SUBSTANCES ACT

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TITLE II—CONTROL AND ENFORCEMENT

PART A—SHORT TITLE; FINDINGS AND DECLARATION; DEFINITIONS

SHORT TITLE

SEC. 100. * * *

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DEFINITIONS

SEC. 102. As used in this title

(1) * * *

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(9) The term "depressant or stimulant substance" means

(A) a drug which contains any quantity of **[**(i)**]** barbituric acid or any of the salts of barbituric acid; or **[**(ii) any derivative of barbituric acid which has been designated by the Secretary as habit forming under section 502(d) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352(d)); or**]**

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